DOES NOT CIRCULATE

Volume 17, Number 2

FEBRUARY 1955

UNIVERSITY OF MICHIGAN
FEB 21 1955
MEDICAL LIBRARY

Postgraduate Medicine

Official Journal
of the Interstate
Postgraduate
Medical Association

Today's Best Treatments at Your Fingertips!

1955 CURRENT THERAPY

See SAUNDERS Advertisement on Pages A-14 and A-15

Tracinets®

BACITRACIN-TYROTHRICIN TROCHES WITH BENZOCAINE

help sore throats feel better, faster

MAJOR ADVANTAGES: Two well-accepted topical antibiotics for local antibacterial effect. Benzocaine for soothing local anesthesia.

Patients like the fast, effective relief TRACINETS bring to sore, irritated throats. When you prescribe TRACINETS, you give your patients the *combined* antibacterial action of bacitracin and tyrothricin. The benzocaine gives soothing local relief. TRACINETS are also an ideal supplement to systemic therapy of severe throat infections.

Supplied: Each troche contains 50 units of bacitracin, 1 *mg.* of tyrothricin, 5 *mg.* of benzocaine. In vials of 12.

SHARP & DOHME

Philadelphia 1, Pa.
DIVISION OF MERCK & CO., INC.

Postgraduate Medicine

Volume 17 · Number 2

FEBRUARY · 1955

OFFICIAL JOURNAL OF THE INTERSTATE POSTGRADUATE MEDICAL ASSOCIATION

TABLE *of* CONTENTS

SPECIAL ARTICLES

Collagen Disturbances Encountered in General Practice
WILLIAM S. MIDDLETON, M.D. 107

The Surgical Treatment of Ulcerative Colitis
RICHARD B. CATTELL, M.D. AND BENTLEY P. COLCOCK, M.D. 114

Chronic Ulcerative Colitis in Children
J. ARNOLD BARGEN, M.D. AND ROGER L. J. KENNEDY, M.D. 127

Drug Allergies
CHAUNCEY D. LEAKE, PH.D. 132

Early Ambulation Following Primary Inguinal Hernioplasty
LOUIS T. PALUMBO, M.D. 140

The Appreciation of Flavors
EDWARD C. CLARK, M.D. AND HENRY W. DODGE, JR., M.D. 142

DIAGNOSTIC CLINIC

Diagnosis of Asymptomatic Malignant Disease: A Report of Six and One-Half Years' Operation of the Cancer Detection Center, University of Minnesota
CLAUDE R. HITCHCOCK, M.D. AND J. BRADLEY AUST, M.D. 145

PEDIATRICS IN GENERAL PRACTICE

Preoperative Preparation of the Pediatric Patient
M. DIGBY LEIGH, M.D. 157

Lead Poisoning in Young Children
HEYWORTH N. SANFORD, M.D. 162

Problems in the Surgical Care of Infants and Children
CLIFFORD D. BENSON, M.D. AND PRESCOTT JORDAN, JR., M.D. 170

GENERAL PRACTICE REVIEW

Benign Diseases of the Breast
ROBERT L. SCHMITZ, M.D. 176

(Continued on page A-10)

Thrombo-embolic Accidents
ORMAND C. JULIAN, M.D. 186

SCIENTIFIC EXHIBIT

Combined Ocular and Cutaneous Manifestations of Disease
MANUEL FRANCISCO ALLENDE, M.D. AND PHILLIPS THYGESON, M.D. 192

POSTGRADUATE CONTINUATION COURSES
Southwestern Medical School and University of Colorado

Pleural Effusion
H. FRANK CARMAN, M.D. 203

Diagnosis and Treatment of Acne
JAMES A. PHILPOTT, JR., M.D. 205

BOOK CHAPTER

Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract
JOHN RUSSELL TWISS, M.D. AND ELLIOT OPPENHEIM, M.D. 210

DEPARTMENTS

EDITORIALS 217
Medical Library Aid
The Costs of Medication
Snuffles
The History of Appendicitis

POSTGRADUATE CLINICAL NOTES
31. Leukemia 113

WHAT'S HAPPENING IN MEDICINE ..... Facing A-32-33

YOUR QUESTIONS ANSWERED A-24
Thalamic Syndrome
Anesthesia for Forceps Delivery
"Cord Bladder"
Coombs Test

MEDICINE FROM ABROAD A-34

THE MEDICAL MUSE. Richard Armour A-46

FORENSIC MEDICINE A-48
The Human Skeleton in Forensic Medicine. Part I.
WILTON MARION KROGMAN, Ph.D.

NEW DRUGS AND INSTRUMENTS A-76

DR. PEPYS' PAGES. Morris Fishbein, M.D. A-88

THE MEDICAL BOOKMAN A-116

INDEX TO TECHNICAL EXHIBITS A-132

Collagen Disturbances Encountered in General Practice

WILLIAM S. MIDDLETON*

University of Wisconsin Medical School, Madison

W. S. MIDDLETON

WHEN medical research extends the frontiers of knowledge in a given field, the literature bearing on the advances assumes an atmosphere of unfamiliarity. New terms must perforce reflect the application of new technics and methods. Until its basic concepts become part and parcel of his daily practice, the physician in the field is apt to assume the entire area esoteric and beyond his ken. If it have a practical application, within a short period the alert practitioner will have gained a working knowledge of the subject. His adaptation to the rapidly changing face of medical science is an astounding phenomenon of our profession.

*Department of Medicine, University of Wisconsin Medical School, Madison, Wisconsin.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

Into this category falls the collagen system which has received unusual research and clinical notice in recent years. Connective tissue is made up of cellular and extracellular constituents. The composition of the extracellular structure is rather complex, i.e., collagen, reticulin, elastin and ground substance. By electron microscopy and other methods, collagen has been specifically characterized. The ground substance is gel-like in composition. Its viscosity varies under physiologic and pathologic conditions. Furthermore, its quantitative relationship to the fixed fibrous structures determines a range of consistency from Wharton's jelly of the umbilical cord to tendon. Obviously, hormones influence these differences in health and disease.

The gel-like state of the ground substance is derived from its long-chain polymers. Essentially a polymerized carbohydrate-protein complex, the ground substance yields, on analysis, hyaluronic acid and chondroitin sulfuric acid, among other substances. Although the supportive function of connective tissue must not be minimized, the ground substance plays an even

more vital role in maintaining the interstitial circulation. The lymphatic and blood vascular ramifications serve as the major channels of fluid transport to and from the various tissues. The ground substance is the intimate link of delivery and discharge between the cellular elements and the blood-lymph stream. This function may be compromised or dissipated by depolymerization of hyaluronic acid, a mucopolysaccharide. This threat is widely encountered in nature in the action of hyaluronidase, an enzyme elaborated by the bee, leech, snake and spider and by the mammalian testis.

The spreading property of hyaluronidase is being exploited in the improved absorption of subcutaneous injections and in the correction of paraphimosis and keloid formation. From a practical standpoint the elaboration of hyaluronidase by certain streptococci and other bacteria explains their invasiveness on one hand and their pathologic sequences on the other. The body in turn meets this antigenic property by forming antihyaluronidase.

The physical-chemical alterations in hyaluronic acid lead first to fibrinoid degeneration of the ground substance which is encountered in many conditions. An earlier viewpoint assumed that because fibrinoid degeneration occurred regularly in hypersensitive states, all conditions attended by this histologic change must a priori be allergic. Its incidence has been reported in a host of unrelated pathologic conditions, such as peptic ulcer and burns. Experimentally, fibrinoid degeneration has been produced by mechanical injury, prolonged passive hyperemia, and large doses of desoxycorticosterone, among other means. Such physical-chemical disruption seriously impairs the interstitial circulation. Transport of nutrients to, and of metabolites and other products from the various cells is seriously compromised. Through these changes the collagen fibers early undergo swelling and disintegration. Cytologic response to this initial injury varies with the location and duration. Depending on the tissue and the organ affected, a series of pathologic and clinical entities has been differentiated after the primary fibrinoid degeneration.

Pathologists have resisted the easy recourse to an inclusion of all diseases in which fibrinoid degeneration occurs under the heading of collagen disorders. If its widespread and nonspecific occurrence is borne in mind, some order may be brought to their general consideration. For practical purposes the clinical expressions of collagen diseases may be grouped as follows:

1. Diffuse collagen disorders
   - Scleroderma
   - Dermatomyositis
   - Lupus erythematosus disseminatus
2. Limited collagen disorders
   - Rheumatic fever
   - Rheumatoid arthritis
   - Polyarteritis nodosa
   - Thromboangiitis obliterans
   - Malignant hypertension
   - Idiopathic ulcerative colitis

Diffuse Collagen Disorders

Scleroderma represents the classic example of a diffuse collagen disorder. The swelling and fragmentation of the collagen fibrils is succeeded by cellular and vascular changes. Encroachment on nutrition results in atrophy of the sweat glands and hair follicles. Raynaud's phenomenon may initiate the clinical picture. Edema is succeeded by induration and atrophy of the skin. The tight, inelastic skin leads to contractures and disabilities in the extremities. Respiratory embarrassment may result from rigidity of the chest wall or encroachment on the pharynx or bronchial tree. Marked wasting and eventual starvation may attend pharyngeal and esophageal involvement. Circulatory failure may result from chronic cor pulmonale or from actual invasion of the myocardium in the primary process. Renal involvement is rare. The clinical diagnosis is usually ready. Roentgenologic studies and electrocardiograms may fix the visceral involvement. Biopsy of the skin will conclude the diagnosis. A mortality rate of 10 per cent from inanition and intercurrent infections is encountered.

Dermatomyositis bears little clinical similarity to scleroderma. The fibrinoid changes in the skin and muscle give way to hyaline and waxy degeneration in the latter. Edema

and vacuolar degeneration with atrophy and replacement by connective tissue follow. The constitutional reaction is severe with moderate to high fever and drenching sweats. Exquisite tenderness over the involved muscles, pallor, puffiness of the eyelids, and multiform eruptions dominate the clinical picture. Muscular involvement is singular in the localization to the upper arms and forearms, upper thighs and legs. After the primary stage of firmness, softening of the involved muscles with atrophy and contractures may be anticipated. Invasion of the muscles of deglutition and respiration brings attendant dangers. Slight splenomegaly and lymphadenopathy occur in most patients with dermatomyositis. Slight leukocytosis with eosinophilia prevails. Creatinuria is the rule. Biopsy may be singularly nondiagnostic. A mortality rate of 50 to 55 per cent is reported.

Lupus erythematosus disseminatus is much more common than generally credited. A portion of the responsibility for the submergence of medical knowledge of this condition arose from failure to appreciate its wide dispersion. In addition to the skin, the subcutaneous tissues, myocardium, endocardium, pericardium, pleura, peritoneum, kidney, liver, spleen, central nervous system and synovial membranes have disclosed its lesions. Beginning with an eosinophilic change in the ground substance of the corium, the collagen fibers thicken. Their fragmentation is succeeded by a basophilic change in the staining reaction. Nonbacterial verrucae are encountered near the edge of the valve leaflets and on the mural endocardium. Beneath these are found deposits of eosinophilic ground substance. The myocardium may show focal fibrosis from independent involvement. Minute hemorrhages may appear in the kidneys. The "wire loops" in the glomeruli are especially diagnostic. Marrow depression is almost inevitable.

Overwhelmingly a disease of the female sex in the second and third decades of life, the clinical manifestations of lupus erythematosus disseminatus may be launched by malnutrition, sunburn or exposure. Erythematous plaques may appear in the "butterfly" area of the bridge of the nose, malar eminences and cheeks. Discrete lesions coalesce and spread to involve the supra-orbital ridges, pinnae, upper lip, chin and V of the throat. Equally significant are the deep-seated erythematous areas on the fingertips and toes. Under ill-advised exposure to sunlight and ultraviolet, extremely dangerous exacerbations with hemorrhagic lesions may occur. Alopecia and shallow buccal or palatine ulcers may develop. Extreme prostration and high fever prevail. Delirium and psychoses are common. Arthralgia or actual arthritis is the rule. Retinal edema, hemorrhages and exudates are observed. Pleural, pericardial and peritoneal involvement account for an appreciable percentage of the instances of multiple serositis. Cardiac arrhythmias and murmurs may be anticipated. Microscopic hematuria is among the most directional laboratory findings. Leukopenia (3000 to 6000) is the rule. Hyperglobulinemia is usually observed.

The L. E. cell has assumed great importance in the diagnosis of lupus erythematosus disseminatus. While the incidence of these cells is not universal in active disseminated lupus and they are occasionally seen in other conditions, their presence is presumptive evidence of the diagnosis. After this finding, it must be excluded unequivocally. A high mortality rate still attends this condition.

Limited Collagen Disorders

The limited collagen disorders may have just as clear a title to the generic designation as those of the diffuse group, but in each instance some delimiting factor denies the broader connotation.

Rheumatic fever is pathologically initiated by swelling of the collagen and fibrinoid degeneration or focal necrosis. Within 10 to 14 days the characteristic Aschoff granuloma dominates the histologic picture. These granulomatous lesions prevail in every tissue involved, i.e., subcutaneous tissue, synovial and serous membranes, myocardium, endocardium, blood vessels, lung and brain. The spleen and kidney are rarely involved. Interesting relics of earlier rheumatic invasion are encountered in scarring of the myocardium, valvular deformity (and calcification) and ad-

hesive pericarditis. At times Aschoff bodies are demonstrable in the dense fibrous tissue of "zuckergussleber."

Group A hemolytic streptococci have been authoritatively charged with the responsibility for rheumatic fever, which commonly makes its appearance 10 to 21 days after the subsidence of scarlet fever, tonsillitis or a simple streptococcal nasopharyngitis. Fever, tachycardia, profuse sweating, prostration and migratory articular involvement characterize the clinical course.

The manner of joint participation in rheumatic fever deserves special attention. Allowing for variations, the larger joints are involved by preference. Although monarticular involvement does occur, polyarthritis is the overwhelming rule. The fleeting quality of this invasion is the order. With involvement of new joints in heat, redness and swelling, prior involved joints are released. Furthermore, there is a remarkable freedom from all evidences of earlier inflammation in these joints. Of course, there may be a return of the involvement in the polycyclic form. Epistaxis, sore throat and subcutaneous nodules are part of the rheumatic picture. Cardiac involvement may be anticipated by persistent tachycardia, disappearance of sinus arrhythmia, and persistent murmurs. Before the friction rub of pericarditis makes the diagnosis self-apparent, it should be suspected if delirium and tachypnea supervene. Anemia, leukocytosis and increased sedimentation rate will be reported by the general laboratory. Prolongation of the PR interval and other electrocardiographic changes are common.

Rheumatoid arthritis likewise must be considered in the light of a limited collagen disorder. Its etiology is uncertain. Clearly the earlier emphasis on focal infection was misplaced. Its articular manifestations may best be focused on the inflammatory pannus that covers the synovial membrane. To the articular cartilage this granulation tissue brings increased vascularity. Coupled with this augmented blood supply come the products of inflammation. Softening and atrophy of the articular cartilages occur. Early fibrinous adhesions between the joint surfaces appear and these may be succeeded by fibrous adhesions and later bony ankylosis. Demineralization of the bony joint members obtains, and atrophy of the skin, soft parts and muscles of the affected extremity is inevitable. Contractures and subluxations are common. Trophic changes appear in the skin. The palms and soles are cold and clammy. Subcutaneous nodules are frequently seen.

The inception of rheumatoid arthritis may be sudden and stormy with high fever and other constitutional reactions, but as a rule it is gradual with a single articular involvement or the insidious involvement of several joints. Typically the small joints of the hands and feet are involved first. In the hands the involvement is most marked in the proximal interphalangeal and the metacarpophalangeal joints. The symmetrical, fusiform swelling of the former is characteristic. The distal interphalangeal joints usually are spared. Ulnar deflection of the fingers may be expected. In turn the joints of the feet, ankle, hip, wrist, elbow, shoulder and spine may be involved. Rarely the temporomandibular and sternoclavicular joints are affected. Eponymic designations have been attached to special departures from the rule without clarification of the basic principles. Constitutional symptoms are usually mild to moderate. The local evidences of inflammation in the involved joints fluctuate widely. Heat, redness and swelling are subject to great variations. The swelling is particularly periarticular, and bursal involvement is the rule. The crippling progression of the disease has well earned the designation, arthritis deformans. Slight hypochromic microcytic anemia and leukocytosis are encountered. Hyperglobulinemia with inversion of the albumin-globulin ratio occasionally occurs.

The reported instances of L. E. cells in the blood of patients with rheumatoid arthritis raise the natural question of an erroneous diagnosis. Yet the two conditions, lupus erythematosus disseminatus and rheumatoid arthritis, may so closely blend in their clinical expressions as to make the distinction very difficult at times. Roentgenograms will disclose swelling of the soft parts about the involved joints and narrowing of the joint spaces

with osteoporosis of the bones in the joint.

Passing attention should be paid to Felty's syndrome, since its components give further weight to a wider complicacy of rheumatoid arthritis than mere articular involvement. The classic picture of rheumatoid arthritis is here complicated by anemia, leukopenia and splenomegaly. While the eponym is unfortunate, recent studies indicate that this complication commonly reflects hypersplenia. In a percentage of these cases a marked remission in the hematopoietic phase has attended the use of cortisone and the performance of splenectomy. Clear establishment of a hemolytic factor in the anemia and of megakaryocytic activity in the marrow must be completed before splenectomy is advised.

Polyarteritis nodosa has long been suspect of allergic origin, and experimental as well as clinical evidence supports this thesis. With the advent and indiscriminate use of the sulfonamides and the antimicrobial agents, its incidence has increased apace. Furthermore, a history of asthma is common among its subjects. Fibrinoid degeneration appears in the media of the affected small and medium-sized arteries. Necrosis and hyalinization are further stages of the process. Vascular and perivascular infiltration with monocytes, neutrophils and eosinophils is characteristic. Intimal proliferation may lead to thrombosis, and in the healing phase canalization and organization may be anticipated. Infarction of important viscera may produce clinical symptoms. Aneurysms of microscopic to gross proportions constitute an interesting element.

The pathologic process may be limited to a single vessel, as in temporal arteritis, or to a single organ, or it may be widespread. Such pathologic variability presupposes very diversified clinical expressions. Indeed, a detailed discussion of the clinical potentialities far exceeds the purview of this presentation. The tetrad of Meyer and Brinkman, i.e., chlorotic marasmus, polyneuritis and polymyositis, striking abdominal manifestations (cramps, vomiting, diarrhea, melena and perforation) and renal involvement, has proved invaluable in the diagnostic approach. If to any combination of these symptoms be added an obscure fever and eosinophilia, the consideration of polyarteritis nodosa is inevitable. Rupture of a polyarteritic aneurysm may lead to gastrointestinal, renal, pulmonary or other hemorrhages. Anemia, leukocytosis and eosinophilia are the leading laboratory supports, but the histologic definition of the vascular lesion clinches the diagnosis. The extending knowledge indicates every degree of gravity. Polyarteritis nodosa is not uniformly fatal.

Thromboangiitis obliterans falls into a somewhat different category. Although allergy has been held responsible by many students of the subject, there is no unequivocal evidence to support the position. The racial predilection for Jews and an apparent contributory relationship in tobacco are leads that have afforded no causal clues. The small and moderate-sized arteries are first involved in a lymphocytic infiltration of the intima. Eventually all layers of the vessel are involved. Giant cells, macrophages and neutrophils are added. Endothelial proliferation of the intima, together with the cellular infiltration, induces thrombosis. Invasion of the vasa vasorum completes the arterial injury. Organization of the thrombus with multiple small canaliculi affords histologic evidence of the nutritional handicap to the part. Significantly the arterial involvement is segmental. Migratory thrombophlebitis of the small veins and involvement of nerve trunks are customary sequelae. Vascular involvement is most marked in the legs, but cerebral, coronary, mesenteric and renal arteries are not infrequently affected. Gangrene of the toes and fingers may advance.

Thromboangiitis obliterans runs a relapsing course in which the first harbinger is intolerance to cold. Paresthesias of burning, itching and tingling are conspicuous. Among the several types of pain, intermittent claudication is the most significant. Local tenderness in the course of the involved veins is noted. Eventually pain at rest supervenes. Rubor to lividity of the pendant legs marks the advance of the process. In addition to these color changes, the local temperature will be reduced. Peripheral pulses in the involved arteries will be decreased to absent. Appropriate tests will establish the order of the arterial insufficiency

and the relative contributions of vasospasm and of organic change to the same. Gangrene is a common consequence of thromboangiitis obliterans.

Malignant hypertension—Certain aspects of arterial hypertension require attention in the present relation. Unfortunately there remains some confusion in the nomenclature of hypertension. In the judgment of some workers the qualifying adjective "malignant" should be reserved for those subjects whose kidneys disclose a necrotizing arteriolitis at necropsy. This change is initiated by a hyaline and collagenous thickening of the intima of the arterioles. Necrosis of the intima and minor thromboses succeed. Simultaneously similar changes develop in the arterioles throughout the body.

To the clinician the term malignant hypertension connotes a rapidly advancing condition with inexorable failure of kidneys and heart. Cerebral symptoms may be dominant. Rapid encroachment on vision is common. Not infrequently this ominous course is transplanted on a benign hypertension, so that dramatically a mild and sluggish course is sharply changed to a violent and precipitous decline. Again the progress may be "malignant" from the outset. In one patient, a male 18 years old, the recognized course from its fulminant onset to death lasted only six months. Headache and restlessness may initiate the disorder. Convulsions and coma are late cerebral manifestations. Nausea and vomiting are common. Amblyopia may early lead to amaurosis. Paresthesias and temporary paresis or actual paralysis may supervene. Circulatory incompetence bespeaks cardiac involvement that may determine the fatal outcome. The eyegrounds will show vascular spasm and sclerosis, hemorrhages, exudates and papilledema. Gross evidences of renal insufficiency mount. Anemia is the rule. Azotemia and acidemia obtain. Examination of the urine will disclose albuminuria, red blood cells and casts.

Idiopathic ulcerative colitis—In an entirely different area, limited collagen disturbances may account for idiopathic ulcerative colitis. Its course is not defined, but psychogenic factors are important. The earliest lesion is a submucosal fibrinoid degeneration. The cellular reaction includes round cells, neutrophils and plasma cells. Segmental involvement is the rule, but the rectosigmoid is the area of predilection. Terminal ileitis may attend the colonic involvement. The gross changes in the involved mucosa begin with hyperemia and edema. Ulceration and hemorrhage succeed. Pseudopolypoid changes may occur. Perforation is not uncommon. In the healing process the colon is reduced to a narrowed, inelastic tube by fibrosis and contraction. Carcinomatous transition occurs in a few cases.

The inception of the clinical course may be with mild bloody diarrhea without constitutional symptoms. In other instances the onset may be fulminant with the passage of grossly bloody stools, high fever and marked prostration. Abdominal cramps and tenesmus mark its course, but bloody diarrhea may occur without discomfort. Tenderness over the affected portion of the colon may be anticipated. Occasionally serious hepatic reactions appear. Portal cirrhosis may result. Rheumatoid arthritis is another interesting complication. Erythema multiforme and erythema nodosum have been observed in ulcerative colitis. Anemia and leukocytosis are variable. The blood calcium is reduced and tetany may ensue. Roentgenography and proctoscopy are invaluable aids to diagnosis. Examination of the stools has a negative value in the absence of ova or parasites.

Summary

From this survey the suggested arbitrary division of the collagen disorders into both a diffuse and a limited group appears justified. The diffuse collagen diseases—scleroderma, dermatomyositis and lupus erythematosus disseminatus—fulfill the criteria of a basic and persistently dominant disturbance of the ground substance as their pathologic background. Furthermore, their clinical courses follow the patterns determined by this fundamental change in whatever tissue or organ may be involved. In the limited collagen diseases, involvement of the ground substance is essentially incidental to more dominant

pathologic alterations. In some instances, viz., rheumatic fever, rheumatoid arthritis and idiopathic ulcerative colitis, fibrinoid degeneration may initiate the process, but it is shortly submerged by more characteristic histologic sequences. In certain cases, notably rheumatic fever, the secondary cytologic reaction defines the disease. In others, i.e., polyarteritis nodosa, thromboangiitis obliterans and malignant hypertension, the alterations in the collagen system appear secondary to earlier pathologic changes. The distinct tendency for a restricted field of involvement sets this group apart from the diffuse collagen diseases.

The earlier tendency to assume a common etiology by reason of a similar pathologic change in the collagen system is obviously gratuitous. Increasing experience emphasizes the wide range in both the qualitative and the quantitative manifestations of the collagen disorders. Presently a number of these expressions defy clinical definition by the available methods. Significantly their gravity is of every degree from innocuous to highly mortal.

Treatment of these diseases has undergone sharp modification in recent years. If salicylates in the treatment of rheumatic fever be excluded, the great advance in management of the collagen disorders has been the addition of adrenocorticotropic hormone and cortisone. Although not panaceas, these agents have induced remissions of varying degrees and duration. Complete clinical arrest or cure has been unusual, and maintenance therapy is usually required to hold the advantage. The limitations of as well as the indications for ACTH and cortisone are receiving intelligent evaluation in the clinic and in general practice. Perhaps the greatest contribution of these agents will prove to be their utilization as a research tool in the evolution of our knowledge of these still obscure disorders.

Postgraduate Clinical NOTES

31. LEUKEMIA

In acute leukemia of childhood, the use of methotrexate may result in a temporary cessation of the clinical and morphologic characteristics of the disease. Within a period of 10 to 50 days, one may see disappearance of blast cells in the marrow and peripheral blood, regression of adenopathy and visceromegaly, re-establishment of erythropoiesis, normal leukocyte and platelet production, healing of bone lesions, and clinical well-being. Approximately one-third of those children treated will enjoy a complete or "hematologic" remission, and another one-fifth will sustain appreciable benefit despite the readily demonstrable presence of leukemic cells. The duration of improvement may continue for a few years in isolated instances, but in the average remission, benefit lasts about 10 weeks.

In the acute leukemias of adulthood, results comparable to those encountered in children are disappointingly rare. Although remissions do occur, only 13.5 per cent of 163 adults selected from several reported series experienced any clinical benefit whatever.

J. F. Holland, *Public Health Report*, December 1954, p. 1155

The Surgical Treatment of Ulcerative Colitis

RICHARD B. CATTELL AND BENTLEY P. COLCOCK*

The Lahey Clinic, Boston

In the past, many physicians have held a very pessimistic attitude toward the treatment of patients with severe ulcerative colitis. The condition of patients with the acute, fulminating form of the disease deteriorated and the patients died in spite of everything that was done for them. Many others remained chronic invalids, unable to work or go to school, because of anemia, malnutrition or persistent diarrhea. When in desperation an ileostomy was carried out in such cases, it often failed to prevent a fatal outcome. When the ileostomy was carried out in time and a fatality was prevented, it often seemed that the care of the ileostomy became as much of a problem as the care of the original disease. The ileostomy tended to retract and prolapse. Serious and even fatal alterations in electrolyte balance could occur with alarming rapidity, especially in the early postoperative period. Obstruction of the small intestine was not uncommon. Persistent bleeding, rectal discharge or arthritis often made further surgery necessary.

*Department of Surgery, The Lahey Clinic, Boston, Massachusetts.

It is important, therefore, to point out that this discouraging picture of the treatment of severe ulcerative colitis has entirely changed in recent years. Although it is still true that these patients are seriously ill and may die without the close cooperation of the internist, the gastroenterologist and the surgeon, the mortality rate can be and has been reduced to less than 5 per cent, even for those patients with the severe form of the disease who require surgical intervention. Even more striking is the marked reduction in the morbidity associated with severe ulcerative colitis. Patients who are incapacitated and unable to work or to finish their education can be rehabilitated economically and socially by ileostomy and the surgical removal of the diseased colon.

If it is to be effective, operation must be carried out before these patients become moribund. This means that surgical intervention is indicated when a complication of ulcerative colitis develops that cannot be handled by medical treatment, or as soon as it is obvious that medical treatment will not restore that

patient to normal social and economic activity. One of the main reasons that the present-day surgical treatment of ulcerative colitis is effective is the realization on the part of the internist, gastroenterologist and surgeon of the value of teamwork in the care of these patients. Cooperative management has led to a steady reduction in the mortality and morbidity rates in our hands and in other clinics interested in the treatment of ulcerative colitis.

RICHARD B. CATTELL

Another important reason for the effectiveness of modern surgical treatment of ulcerative colitis has been a continued improvement in surgical technic. Appendicostomy, cecostomy and colostomy were found to be unsatisfactory and have largely been abandoned. Ileostomy and colectomy remain the only effective means of surgical intervention in this disease. Further experience has shown that many of the complications of ileostomy, such as prolapse, retraction, skin irritation and electrolyte imbalance can, to a large extent, be prevented by careful construction of the ileostomy and by close observation of the patient during the early postoperative period. The modern ileostomy bag, which is cemented to the skin, eliminates odor and fecal soiling, is flat and can be worn unnoticed even under a form-fitting dress, and permits these patients to take part in normal social and economic life with confidence. A well-fitting ileostomy bag and the complete rehabilitation of these patients are completely dependent on a well-constructed ileostomy.

Surgical Treatment

Ulcerative colitis is a nonspecific inflammatory disease of unknown etiology. It usually begins in the distal colon or rectum and progresses proximally by direct continuity, involving all coats of the bowel wall. In about 10 per cent of the cases the distal small intestine is involved. It is characterized by exacerbations and remissions. Occasionally, the intervals of remission are prolonged, and any form of treatment can be evaluated only after a long follow-up period.

BENTLEY P. COLCOCK

The disease is most frequently found in the Temperate Zones and is rare in the tropics. Among the factors that may play a part in its origin are food sensitivity, spasm of the smooth-muscle coats of the bowel wall, preexisting infection such as amebic or bacillary dysentery, psychosomatic disorders and, possibly, abnormal function of the sympathetic nervous system. All of these factors have a bearing on the medical and surgical treatment of this disease.

The number of patients who will be considered failures of medical management depends on the extent, severity and duration of the disease. As more of these patients are followed for longer periods, complications which require surgical treatment will develop in more cases, and there will be a larger group of patients who cannot regain their normal health by any amount of medical therapy. In order to lower the morbidity and the mortality associated with the medical treatment of this disease, an increasing number of these seriously ill patients must be submitted to operation. In an earlier report, only 25 per cent of our patients with ulcerative colitis were operated on, and in the group now being reported, approximately 50 per cent require surgical intervention.

It should be emphasized that when the surgeon accepts these patients for treatment he assumes responsibility for their care for an indefinite period which may be for the lifetime of either the patient or the surgeon. Any patient with an ileostomy is exposed to certain hazards concerning which he may need advice or treatment at any time throughout his life. Unwise advice or treatment by physicians unfamiliar with the care of a patient who has an ileostomy may precipitate a serious compli-

cation. Fortunately, most patients become quite expert in the care of their ileostomy, and serious trouble rarely occurs.

Indications for Surgery

Acute fulminating ulcerative colitis—It is in this group that the greatest number of medical and surgical deaths occur. Some patients respond to complete rest, blood transfusions and administration of antibiotics and ACTH. Others do not, and continue to fail rapidly and die, sometimes within a few days. In our experience, ileostomy will save some of these patients who would otherwise die, provided it is not carried out too late. They require daily, if not hourly, consultation between the internist and the surgeon. From 1928 to 1946, 147 ileostomies were done with 26 deaths, a mortality rate of 18 per cent. This high rate was largely the result of delayed acceptance of surgery. The over-all mortality rate in 219 patients operated on between 1947 and 1952 was 5 per cent.

Bleeding—Fortunately, profuse hemorrhage in ulcerative colitis is rare. When it does occur and fails to respond to bed rest and repeated transfusions, ileostomy should be done (figure 1). Occasionally, even defunctionalizing the ulcerated colon by an ileostomy will not stop alarming bleeding, and these patients may need a colectomy within a few days in spite of the appreciable operative risk involved. A much more common indication for surgery is persistent moderate bleeding which results in a marked secondary anemia in spite of intensive medical treatment.

Perforation—Perforation into the free peritoneal cavity is uncommon, but may occur during an attack of acute fulminating ulcerative colitis. When it does occur, little can be done for these patients except to treat them for generalized peritonitis. An ileostomy should be done as soon as their general condition permits. Any residual peritoneal abscesses should be drained.

Subacute or chronic perforation is more common and most frequently occurs in the rectal segment, leading to fistulas between the rectum and perineum, the rectum and vagina, and occasionally between the rectum and bladder (figure 2). Local operative procedures for the common perineal fistulas are contraindicated for they may result in rectal incontinence if this is not already present. Resection of the colon and rectum is necessary for a cure.

Infectious arthritis—Infectious arthritis is a serious complication of ulcerative colitis. Even though the other symptoms of the disease may be brought under control, the inflammatory reaction in the joints may persist and may lead to serious deformity and permanent loss of function. We believe that the development of infectious arthritis in a patient with ulcerative colitis is in itself an indication for ileostomy and colectomy (figure 3). If the diseased colon is removed before permanent changes occur in the joints, the arthritic symptoms are completely relieved.

FIGURE 1. The patient, aged 26 years, had had ulcerative colitis for two years, with repeated rectal hemorrhages requiring many transfusions. Extensive ulceration of the colon, particularly of the ascending colon, may be seen on this barium enema film. Bleeding was stopped by ileostomy and subtotal colectomy.

FIGURE 2a. Extensive ulcerative colitis present on barium enema study, November 1950.

FIGURE 2b. Barium enema March 1951 shows increased contracture of the colon due to progressive ulcerative colitis. The patient was 23 years old, and the duration of the disease was five years. Profuse diarrhea and many rectal abscesses necessitated several rectal operations which resulted in complete rectal incontinence.

Obstruction—Repeated exacerbations and remissions of chronic ulcerative colitis lead to extensive fibrosis and scarring. The lumen of the colon becomes markedly narrowed, and this narrowing may lead to varying degrees of obstruction (figure 4). The healing of the ulcerative process that follows ileostomy may result in almost complete obliteration of the lumen in certain areas of the colon. Even though these patients may be completely relieved of their symptoms by the ileostomy, their colon is useless so far as resumption of normal function is concerned and should be removed.

Carcinoma—The longer the physician follows patients with chronic ulcerative colitis, the more concerned he is about the complication of malignant degeneration in the diseased colon. The over-all incidence of carcinoma in ulcerative colitis is probably less than 5 per cent. In those patients who come to surgery, it rises to approximately 10 per cent, and in that group of patients who have had the disease for 10 years or more it has been found to range from 25 to 50 per cent. Cancer in the presence of ulcerative colitis has an extremely poor prognosis. The symptoms of carcinoma of the colon—namely, pain, bleeding and a change in bowel habit—pass unnoticed, for these patients have had these symptoms for years. The marked increase in vascularity of the chronically inflamed colon permits the early and rapid spread of the carcinoma.

We believe, therefore, that any patient who has had the signs and symptoms of chronic ulcerative colitis for 8 to 10 years or more should have regular check-up examinations of his rectum and colon, even though his symptoms may be relatively quiescent. In addition to proctoscopic and barium enema examinations at regular intervals, he should be warned to return immediately if there is any sudden

FIGURE 3a. Barium enema film showing extensive ulcerative colitis with marked fibrosis and contracture of the colon.

FIGURE 3b. Knee joint, showing no destruction of the joint cartilage in spite of severe pain in both knees. The patient, aged 45 years, had symptoms of severe diarrhea, rectal bleeding and increasing arthritic pain. Ileostomy performed in August 1946 did not relieve the arthritis. Subtotal colectomy was done in February 1947; joint pain was much improved. After abdominoperineal resection in June 1947, joint pain was completely relieved.

increase of rectal bleeding, the development of localized pain or an abrupt change in the usual number of daily stools. Any patient with ulcerative colitis whose disease is severe enough to require an ileostomy should also be advised to have a total colectomy within a few months unless his disease is of short duration (figure 5).

Intractability to medical management—In addition to the above indications, a considerable number of patients with ulcerative colitis require surgical intervention because they fail to respond to any form of medical treatment. They become economic cripples because of malnutrition, chronic anemia or severe, persistent diarrhea. Their symptoms fail to clear up sufficiently for them to return to work, or promptly recur when they do return to work. They may be incapacitated by an incompetent anal sphincter, which may make it impossible for them to stay at their jobs or continue in school. In recent years the internist, gastroenterologist and surgeon have learned to recognize patients of this type and to realize that they can be rehabilitated by ileostomy and colectomy (figure 6).

Surgical Management

Since any patient with chronic ulcerative colitis severe enough to require surgical intervention is rarely a good operative risk, he should be prepared as carefully as possible. A high caloric diet, with supplementary vitamin intake, adequate fluids, antibiotics and transfusions, is important. In some cases a short course of ACTH will improve the patient's general clinical condition, although in our experience this improvement is temporary and use of this drug has not decreased the number who eventually require an operative procedure for ulcerative colitis.

We prefer spinal anesthesia (PONTOCAINE®,

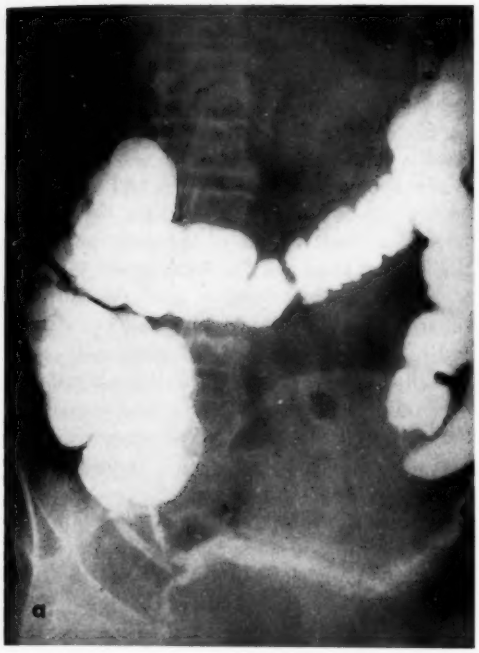


FIGURE 4a. Barium enema study of colon showing marked narrowing of the rectum and sigmoid colon due to cicatrization.

FIGURE 4b. Resected specimen, showing site of previous colostomy and contracted distal colon. Patient, aged 59 years, had the disease for eight years. Colostomy was done elsewhere in June 1951 for large bowel obstruction. The patient continued to have rectal bleeding and abdominal pain. Ileostomy and colectomy were carried out in March 1953; patient is well.

glucose or fractional spinal) because it permits minimal manipulation of the small bowel and colon at the time of operation.

The only surgical procedures that have proved to be effective for the great majority of these patients are ileostomy and total colectomy. In a few cases in which disease is confined to the right colon, resection of the right colon alone may be carried out. This may be combined with an immediate anastomosis of the terminal ileum to the sigmoid colon or with the establishment of an ileostomy. Several months later, intestinal continuity may be restored if the residual colon and rectum have remained free of disease. Occasionally, when the disease is confined to the rectum and sigmoid, it may be possible to relieve the symptoms by a left hemicolectomy and ab-

FIGURE 5. Barium enema study, showing extensive ulcerative colitis but no evidence of malignant degeneration.

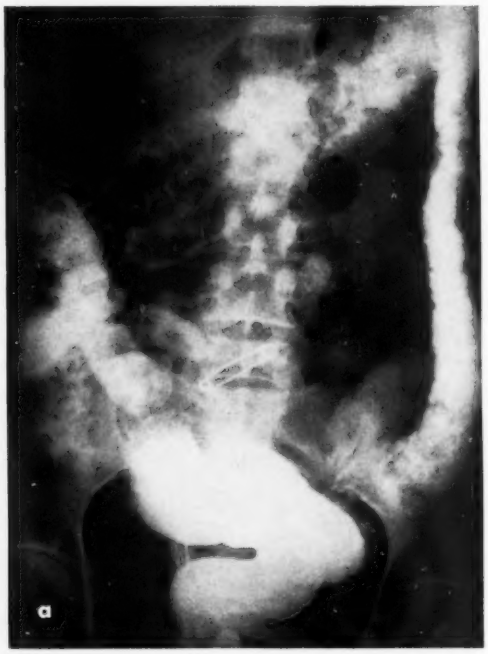


FIGURE 6a. Barium enema study showing pseudopolypoid degeneration produced by areas of mucosa separated by scars.

FIGURE 6b. Resected specimen showing the pseudopolypoid formation. Patient was 30 years old. The symptoms were diarrhea, bleeding and abdominal pain, with poor response to bed rest, penicillin, transfusions and ACTH. Ileostomy and total colectomy were performed and the patient is now well.

dominoperineal resection, bringing out the distal transverse colon as a colostomy. The main difficulty with segmental resection of the colon for ulcerative colitis arises from the fact that it is almost impossible to determine by proctoscopic examination, by barium enema study and even by palpation and inspection of the colon at operation where the disease begins and ends. Most of these patients eventually have required ileostomy and total colectomy because of extension of the disease and recurrence of symptoms (figure 7).

Restoration of intestinal continuity occasionally is considered when the patients obtain relief of their symptoms and regain normal health and strength following ileostomy alone. Before eliminating the ileostomy and restoring intestinal continuity, we have always insisted that the patients have a complete remission of all symptoms with no rectal discharge for at least one year, and that they have negative sigmoidoscopic examination and normal flexibility of the colon, as demonstrated

FIGURE 7a *(below)*. Barium enema film showing rigid, fore-shortened colon with loss of almost all normal mucosa.

by barium enema study. In spite of these rigid criteria, half of the patients in whom we have closed the ileostomy have had a recurrence of symptoms within five years and have required a second ileostomy. For these reasons we believe that all but a few patients with chronic ulcerative colitis who come to surgery will require ileostomy and complete removal of their colon and rectum.

Two-thirds of our patients have had three operative procedures, that is, ileostomy followed by subtotal colectomy followed by abdominoperineal resection. The remaining third have had ileostomy and subtotal colectomy at the first operative procedure, followed later by abdominoperineal resection for removal of the sigmoid and rectum. In recent years, Miller, Crile, Ravitch and others have advised that colectomy be done at the same time as ileostomy in all patients with ulcerative colitis coming to surgery. They believe that even the extremely toxic patient has a better chance for recovery if his diseased colon is removed than if it is left in place, even though it is defunctionalized. We have not adopted this plan for two main reasons: First, we do not believe that we can do an ileostomy and a colectomy in these poor-risk patients with as low a mortality rate as with an ileostomy alone. Second, except for a small group of patients who are bleeding and who continue to bleed, if the patient survives his ileostomy he will regain his weight and strength and the colectomy can be carried out two to three months later on a good-risk patient with a well-functioning ileostomy. If the patient is not severely ill and is in the chronic cicatricial stage of his disease, however, the colon can be removed down to the sigmoid at the same time the ileostomy is established, with a reasonably low mortality rate.

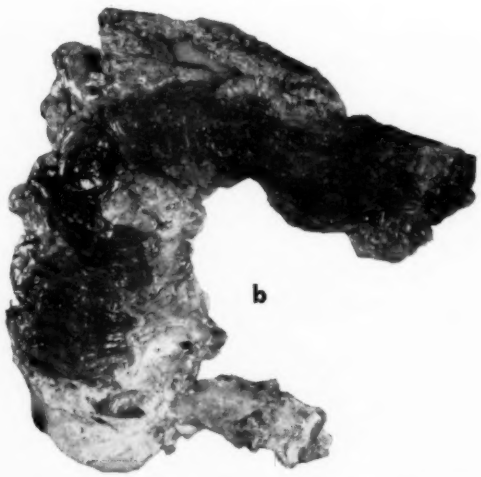


FIGURE 7b *(above)*. Resected specimen showing contracted ascending, transverse and descending colon. Patient was 54 years of age; duration of disease was six months. Abdominal pain, diarrhea and rectal bleeding increased despite use of ACTH, cortisone and all forms of medical treatment. Distention and symptoms of obstruction occurred due to contracture of the left colon. Patient is now well following ileostomy and subtotal colectomy.

Ileostomy

In a seriously ill patient the simplest possible type of ileostomy is carried out. A loop of terminal ileum proximal to any disease is delivered and divided, and a catheter inserted in the proximal end (figure 8). Many ileostomies of this type require subsequent revision. Here, however, we are concerned with saving a patient's life by defunctionalizing his diseased colon with a minimal amount of operative trauma.

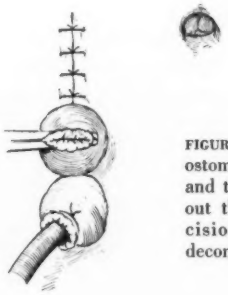


FIGURE 8. Double-barreled ileostomy. The bowel is divided and the two ends are brought out the lower end of the incision. Functional ileum is decompressed.

The majority of even the toxic patients will tolerate the establishment of a carefully constructed permanent ileostomy. A small right rectus incision is made so that when the functioning ileum is brought out the lower end of the incision, the ileostomy will be placed ap-

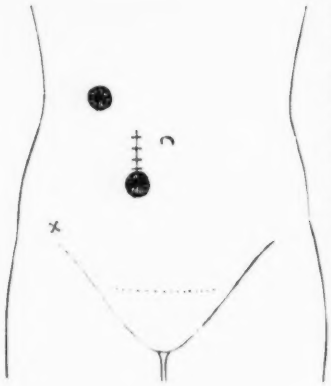


FIGURE 9. Divided ileostomy. Functioning loop is brought out through the lower end of right rectus incision, nonfunctioning loop is above and to the right where it may be incorporated in the subsequent transverse incision.

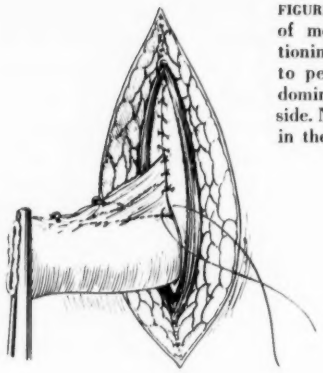


FIGURE 11. Peritoneum of mesentery of functioning ileum is sutured to peritoneum of abdominal wall on each side. No suture is placed in the bowel wall.

proximately 2 in. below the umbilicus and 1½ in. to the right (figure 9). We prefer this to a stab wound at this point for it permits better fixation of the mesentery. In any event, the ileostomy must be placed so that it will permit secure fixation of the ileostomy bag. This means that the bag must not overlie the umbilicus, the pubic hair or the anterior superior spine.

The abdomen is not explored, for even gentle handling of the diseased colon will lead to some degree of peritonitis and may result in perforation. The terminal ileum must be divided well proximal to any involvement of the small bowel by the inflammatory process. This will usually mean a point 6 to 8 in. from the ileocecal valve and may be higher if there is more than the usual amount of involvement of small bowel. The mesentery of the ileum is divided in a vertical manner for a distance of 3 in. and then at right angles to this for a short distance to avoid any curvature in the ileostomy as a result of the pull of the mesentery (figure 10).

Since closure of the nonfunctioning ileum would produce a closed loop if stenosis of the colon is present, it is exteriorized. We prefer to bring it out through a stab wound above and to the right of the right rectus incision where it can be incorporated in the transverse incision which is used for the subsequent colectomy. Prolapse or retraction of the ileostomy can be prevented by careful fixation of the mesentery of the ileum to the peritoneum of the abdominal wall (figure 11). It is unwise to attempt fixation of the ileostomy

FIGURE 10. Point for division of ileum is selected proximal to the inflammatory process. Transverse division of the mesentery prevents angulation of functioning ileostomy.

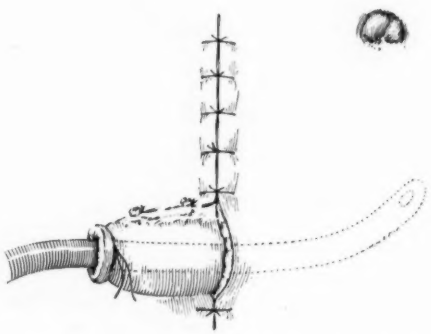


FIGURE 12. Ileum is decompressed by insertion of a large, soft catheter into the bowel after the incision is closed.

by suture to the bowel wall itself since, in the presence of ulcerative colitis, sutures in the bowel wall often lead to fistulas. A fistula at or below the skin level will so interfere with adequate fixation of the ileostomy bag that revision of the ileostomy will be inevitable. The ileum should project 1½ to 2 in. above the level of the skin so that subsequent retraction will lead to an ileostomy approximately 1 in. in height which will project comfortably into the ileostomy bag.

After the wound has been closed and dressings applied, the ileum is decompressed with a large, soft rectal tube held in place by a purse-string suture (figure 12). The rectal tube is connected by tubing to a bottle at the side of the bed and will keep the wound dry until it is removed in four to five days. The initial dressing is not disturbed during this time, which also helps to secure adequate fixation of the ileostomy. The application of compound tincture of benzoin to the skin is begun in the operating room. Experience has shown that it is much easier to prevent skin irritation than it is to treat it once it has occurred.

The ileostomy will usually begin to function in 24 to 36 hours following surgery. Once the ileostomy begins to function, its drainage may remove large amounts of fluid including large amounts of potassium and chloride. If these fluids are not replaced promptly, serious and rapid deterioration of the patient's condition will occur. When the ileostomy contents begin to thicken around the fourth to fifth day following surgery, the indwelling catheter is removed and a temporary type of plastic bag is cemented to the skin.

At the end of a week the ileostomy is measured for a permanent ileostomy bag which the patient begins to wear before he is discharged from the hospital. This bag has a plastic ring which permits the size of the aperture to be decreased later when the ileostomy has retracted to its permanent size (figure 13). The rubber bag is detachable and replaceable. Later, if he desires, the patient may change to one of two other types of permanent ileostomy bags which we have found to be very satisfactory.

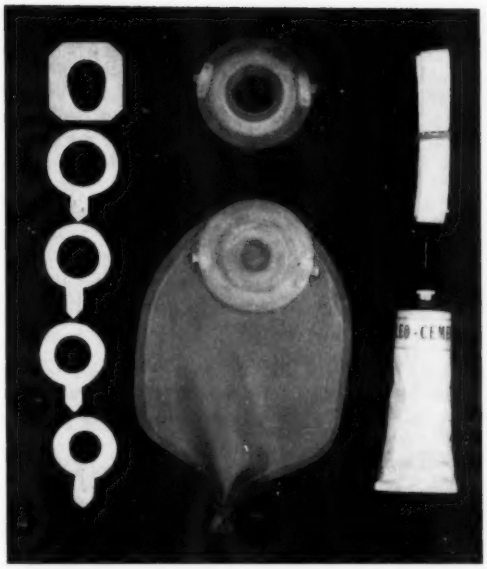


FIGURE 13. One type of permanent ileostomy bag with detachable plastic ring. Size of opening can be changed by filling with plastic and reboring.

In patients whose condition will permit subtotal colectomy at the same time that the ileostomy is done, a longer right rectus incision is made and the right colon, transverse colon and descending colon are resected. The right and left lateral gutters are reperitonealized, the terminal ileum brought out at the proper place for the ileostomy, and the distal colon exteriorized through a stab wound to the left of the umbilicus (figures 14a and b). Colon that is involved in the ulcerative process cannot be closed securely and it is much safer to exteriorize the distal segment than to attempt to close it and leave it within the abdomen (figures 15a and b).

Colectomy

The average interval between ileostomy and subtotal colectomy is approximately three months. By this time patients have usually gained 20 to 30 lb. in weight, are having very little discharge from the rectums and represent good surgical risks. Occasionally, if significant bleeding continues, the colectomy must be done before this time. If arthritic

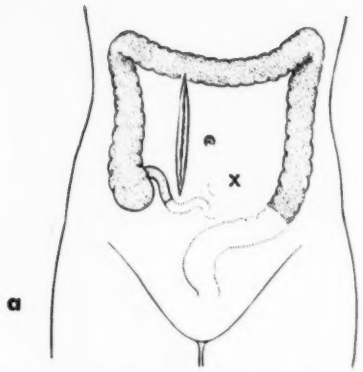


FIGURE 14a. Shaded area shows extent of ileum and colon to be removed. Distal colon will be implanted in a stab wound at point X.

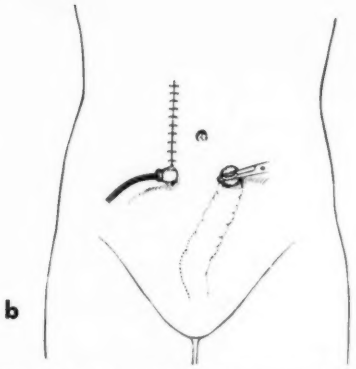


FIGURE 14b. Site of functioning ileostomy and implantation of distal colon. The implanted colon will be included in the abdominoperineal resection which is done through a left paramedian or left rectus incision.

symptoms are prominent it is well not to defer the colectomy beyond six to eight weeks. On the other hand, if the patient is in good condition and is having little activity from his rectum, the subsequent operative procedures may be arranged to suit his convenience. Occasionally we have deferred the colectomy several months pending completion of the school year or of other important work the patient may have planned.

Subtotal colectomy is carried out through a transverse incision which incorporates the nonfunctioning ileostomy. If a double-barreled ileostomy is present, the distal loop of ileum is closed beneath the peritoneum unless revision is required for any reason (figure 16).

Since the rectum is involved in practically all cases of severe ulcerative colitis, the final stage of the operative treatment is abdominoperineal resection. This may be either a second or a third operative procedure. The dissection is kept close to the bowel wall unless there is reason to suspect the coexistence of carcinoma. Drainage from the perineal wound may continue for a considerable length of time, but if adequate drainage is maintained, solid healing will occur eventually.

All these patients are instructed to report promptly any abnormal functioning of their ileostomies. Mild degrees of obstruction to

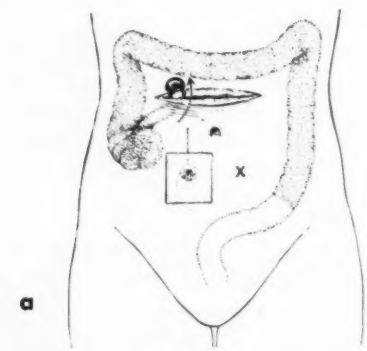


FIGURE 15a. Transverse incision incorporating the nonfunctioning ileostomy. Shaded area shows extent of resection. Tape covers the functioning ileostomy during operative procedure. X indicates point of stab wound for implantation of distal colon.

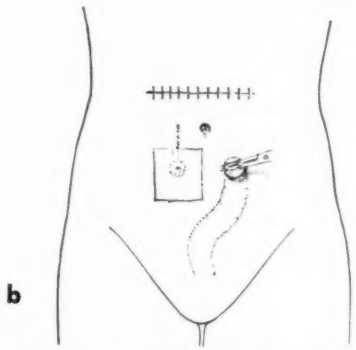


FIGURE 15b. Tape is removed from ileostomy and ileostomy bag again applied. Distal colon is held in place by a clamp incorporated in dressings.

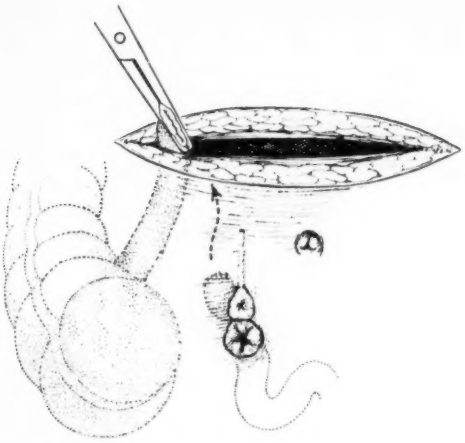


FIGURE 16. If double-barreled ileostomy has been done, the nonfunctioning loop of ileum is closed beneath the peritoneum unless revision is indicated.

ileal drainage, if treated early by catheter irrigation, will usually subside spontaneously. If allowed to go on, and if edema and dilatation occur in the bowel, laparotomy may be required to relieve the obstruction. Excessive functioning, with large amounts of watery discharge, may indicate partial obstruction of the jejunum or upper ileum. Later, excessive functioning of the ileostomy may be the result of inflammatory changes in the distal ileum due to regional ileitis. If this persists it may be necessary to revise the ileostomy, bringing out a higher portion of the ileum, with removal of the diseased bowel.

Revision of the ileostomy may also be necessary if a fistula develops in the side of the ileum sufficiently low to prevent proper adherence of the ileostomy bag. We have not thought it advisable to skin graft these ileostomies. By repeated gentle dilatation, an adequate opening is maintained during the early postoperative period. If the ileostomy has been properly constructed in the beginning, it will project well into the ileostomy bag and, at the same time, being soft and compressible, it will not form a noticeable protuberance on the abdominal wall.

Clinical Data

In the 25 year period from 1928 to 1952, 871 patients with ulcerative colitis have been treated at the Lahey Clinic. All these patients have been under the care of the Department of Gastroenterology and were given a fair trial on bed rest and intensive medical management. Of this entire group, 413 patients, or 47 per cent, required surgical intervention for one of the reasons previously discussed. These 413 patients had a total of 858 operative procedures (table 1). To illustrate the striking improvement that has taken place in the surgical management of ulcerative colitis, this total group of patients has been divided into two groups of roughly comparable size. In the 19 year period between 1928 and 1946, 194 patients were operated on, with 43 deaths or a mortality rate of 22.2 per cent. In the six year period between 1947 and 1952, 219 patients were operated on with 11 deaths or a mortality of 5 per cent (table 2). This high mortality in the earlier group was due to a large extent to the fact that they were submitted to ileostomy too late. This is indicated by the operative procedure mortality.

In the earlier group, operated on between 1928 and 1946, 313 operative procedures were carried out, with 43 deaths or a mortality rate of 13.7 per cent (table 3). This figure is for the same group in which the over-all mortality was 22.2 per cent. In other words, if the patients operated on during this period

TABLE 1

SURGICAL TREATMENT
(1928-1952 inclusive)

Total patients seen	871
Total patients operated on	413
Total operations	858

TABLE 2

PATIENT MORTALITY

YEAR	CASES	DEATHS	
		Number	*Per cent*
1928-1946	194	43	22.2
1947-1952	219	11	5.0

TABLE 3

OPERATIVE PROCEDURE MORTALITY

YEAR	OPERATIONS	DEATHS	
		Number	*Per cent*
1928-1946	313	43	13.7
1947-1952	545	11	2.0

survived their ileostomies, they usually survived their colectomies and abdominoperineal resections. This is also true for the later group. Of 545 operative procedures performed on patients with ulcerative colitis between 1947 and 1952, there were 11 deaths, an operative procedure mortality of 2 per cent (table 3). This is also well illustrated by the drop in the mortality for the two groups following ileostomy alone. In the earlier group, the mortality following ileostomy was 17.7 per cent. In the second group operated on between 1947 and 1952, the mortality for ileostomy was 4.3 per cent (table 4).

TABLE 4

ILEOSTOMY MORTALITY

(355 Patients)

YEARS	CASES	DEATHS	
		Number	*Per cent*
1928-1946	147	26	17.7
1947-1952	208	9	4.3

Illustrating the point that the surgical management of these patients is not complete when they have recovered from their operative procedure and have left the hospital is the fact that in this group operated on between 1947 and 1952, there have been seven deaths since these patients were discharged from the hospital (table 5). These deaths occurred within a few months of their discharge and were attributable in most instances to delay in treating some complication of ileostomy or ulcerative colitis on the part of either the patient or the family physician. We believe that most of these deaths were preventable. If this mortality is added to the postoperative mortality, we have an over-all mortality rate of 8.2 per cent for the 219 patients operated on between 1947 and 1952.

TABLE 5

MORTALITY 1947-1952

(219 Cases)

	Number	*Per cent*
Postoperative deaths	11	5.0
Late deaths	7	3.2
Total (219 cases)	18	8.2

Summary

Surgical treatment will permit the social and economic rehabilitation of patients with severe ulcerative colitis who fail to respond to medical treatment or in whom a complication of ulcerative colitis develops that cannot be treated medically.

If surgical intervention is carried out when indicated, it is associated with a low mortality rate and a decided decrease in the morbidity associated with patients in this group. The indications for surgical intervention have been reviewed.

Ileostomy and colectomy represent the only effective surgical treatment for patients with severe diffuse ulcerative colitis. The complete rehabilitation of these patients is dependent on a properly constructed ileostomy. Our technic for ileostomy and colectomy has been presented. Our experience with 413 patients who were operated on for ulcerative colitis between 1928 and 1952 has been reviewed.

Chronic Ulcerative Colitis in Children

J. ARNOLD BARGEN* AND ROGER L. J. KENNEDY**

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

ALTHOUGH quite a number of publications on chronic ulcerative colitis had appeared in the literature prior to the report published by Helmholz[1] in 1923, it was he who first described the disease as it affects children. This report dealt with only five cases. In 1940 Jackman, Bargen and Helmholz[2] reported on the life histories of 95 children with chronic ulcerative colitis. This represented approximately 11 per cent of the patients coming to the Mayo Clinic with this condition between the years 1925 and 1931, inclusive. Thus, it would seem that one of every nine patients suffering from chronic ulcerative colitis as it is encountered at the clinic is afflicted by the disease between the ages of 1 and 15 years, inclusive. It was noted then that one of every 274 patients encountered in the Section of Pediatrics had chronic ulcerative colitis, developing during infancy or childhood. It was noted also that among those cases in which the month of onset of the disease could be elicited definitely, in the majority the onset as well as the relapses occurred during those months in which infections of the upper respiratory tract are especially prevalent.

J. ARNOLD BARGEN

ROGER L. J. KENNEDY

It was found that although the disease is basically the same in childhood as it is in later life, it is likely to be more severe and the response of the patient to treatment is less satisfactory than in adults. The following com-

*Section of Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

**Section of Pediatrics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

The Mayo Foundation in Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

plications of the disease were noted among the 95 children: polyposis, stricture, anal abscess, fistula, arthritis, erythema nodosum, perforation, carcinoma of the colon, phlebitis, splenomegaly, nephritis, massive hemorrhage, endocarditis, pyelitis, and others.

It was also found that when a child became ill with this disease in early infancy, diminished growth and development of the entire body occurred if the disease had been present for a long time during the formative years of childhood and adolescence. Benson and Bargen[3] reported on this phase of the disease in 1941. They noted sexual and somatic retardation among these children, which on some occasions was strikingly severe. It was noted that if the child was seen when the disease was in a stage of lesser activity, the lack of development so dominated the clinical picture that the problem might be confused with infantilism of endocrine origin.

As a background for this report, the records of the patients coming to the clinic for examination or treatment or both during the decade including January 1, 1944 through December 31, 1953 have been reviewed. This represents a group of 139 children in addition to those previously reported. We shall discuss some of the details of the nature of the illness, the length of time that the patients have had trouble, the changes in treatment, and the present status of the difficulty.

It is interesting to note that in 25 instances among the 139 children, the disease occurred in an only child of a family. When there were two children in the family, in about half of the instances the patient was the first child, and in the other half he or she was the second child. Moreover, in a family of 12 children the patient was the ninth. The disease seemed to be commoner in boys than in girls by a ratio of 86 to 53. The commonest age of onset of the disease was 8.6 years, although in six children the disease began between the ages of one and two years. In only 10 did it begin between the ages of 13 and 14 years.

It might be of some interest to note that in 20 cases the illness had existed for less than six months when we saw the child. In 35 it had been present for one to two years, and in four it had been present for seven to eight years. Chronic ulcerative colitis may remain mild and not disabling to these children for months or years, but it is inclined to progress in severity so that while the disease might start in a mild fashion, and indeed did so in 26 cases, the illness was very severe when we saw the patient. However, in only five instances was the onset of the illness of the fulminating variety, namely, with high fever, extreme toxemia, massive rectal hemorrhages and severe diarrhea.

The proctoscopic appearance of the lesions varied from so-called mild (grade 1) to very active disease (grade 3), six being of the former and eight of the latter, but in 64 patients the disease was graded as having an activity of 2 (on the basis of 1 to 4). In the so-called mild cases, there was simply the granular, easily bleeding mucous membrane with the complications of secondary ulceration. In those graded as 3, there was the granular mucosa plus edema, intermucosal hemorrhages, huge sloughing secondary ulcers and, at times, perirectal abscesses and fistulas.

The roentgenologic involvement of the large intestine in these children was of particular interest. In only 11 was the rectum alone involved; in four, the rectum and sigmoid; in six, from the anus to the splenic flexure; in six, to the hepatic flexure; and in 96, the entire colon. In 13 of the latter, the terminal ileum was also involved. Of 96 patients in whom the entire colon was involved the disease was reported as very severe and destructive in 21. In six of these children the involvement was segmental in that segments of the large intestine above the sigmoid were involved without involvement of the rectum.

Complications

Serious complications of the condition occurred among a relatively small percentage of these children. Only 12 of these children had rectal polyps, and in two of them carcinoma developed, one at the age of 17 years and the other at the age of 18 years. In the patient of 17 years, the carcinoma was multicentric, grade 4, of a scirrhous type with tubular involvement of the entire ascending colon. In

the other there were multiple grade 1 adenocarcinomas in the rectum and sigmoid.

It has been found that carcinoma occurs many times more frequently in patients who have had ulcerative colitis than in other human beings, but we must not lose sight of the fact that carcinoma of the colon in children of this age is ordinarily, and for practical purposes, nonexistent.

Two of these children had liver disease with severe hepatitis followed by cirrhosis. Four had arthritis. In three, perirectal fistulas developed. In six there was failure of growth and of development of secondary sex characteristics so that the children later on appeared in a state of pseudodwarfism. In 26 there was chronic invalidism, and in 24 others complications of one type or another developed, including rectal stricture, pyoderma gangraenosum of the skin and other less common conditions.

In the last half of this study a considerable number of these patients were submitted to psychiatric investigation. We are not aware that this developed any substantial information about the nature of the illness, nor did it give important impressions about therapy.

In the early part of this study, NEOPRONTOSIL® was the drug commonly prescribed. Later, phthalylsulfathiazole (SULFATHALIDINE®) was employed, and in the latter part of the study, salicylazosulfapyridine (azopyrin, azulfidine) was used extensively. It is very apparent from our observations that the results from treatment with the latter drug far exceed those of any previous drug used.

It is of particular interest to know that 67 of these patients had blood transfusions as part of their treatment. In two of them, hemorrhage was so massive and intractable that 22 transfusions were necessary in each case before the condition was controlled. In 34 children only one transfusion was given and in the others a variable number.

Six of these children underwent operation, two because of carcinoma. One patient underwent ileostomy because of chronic invalidism, another because of cholangiolitic cirrhosis with jaundice. A fifth had undergone colectomy elsewhere for reasons not apparent at the time of this study, and a sixth patient had undergone first colostomy and later ileostomy elsewhere.

Eight of these children died, two being among the six who had undergone operation. One was the child with the multicentric grade 4 carcinoma, who died a month after colectomy. Another was the child who had undergone ileostomy because of general debility. In the child who had undergone colectomy in the hope of staying the cirrhosis, the cirrhosis progressed without interruption. The other five deaths were among patients who had not undergone operation. One was a child with a fulminating illness who died on the tenth day after admission to the hospital from an overwhelming toxemia. Another died after 20 days in the hospital with perforation and general peritonitis. A third child with a fulminating illness died after 77 days in the hospital with hepatic failure. A fourth with intestinal obstruction died at home. Both the third and the fourth child had a daily elevation of temperature to 104° or 105° F. during their entire stay so that at no time would it have been feasible to consider surgical intervention. A fifth child died at home from an accident.

Follow-up

For 40 of the 139 patients, close and recent personal observation was available. Of these 40, six had died, four had undergone operation at the clinic, two were totally uncooperative, and 10 were greatly improved but had been observed for a period shorter than two years. In 18 who had been observed for two years or more, the last recent examination at the clinic showed the condition healed as observed by proctoscopic observation as well as by roentgenologic examination. In other words, in 18 of the 40 patients all evidence of their previous colitis had disappeared, and 10 others were greatly improved or felt well.

Letters of inquiry were sent to the other 99. To date, two and one-half months since the letters were sent, 86 replies have been received and four letters have been returned as unclaimed. Among the 86 patients for whom we have information from the follow-up letters, five others had died. Three patients died

as a result of complications of colitis, one was burned to death in a college dormitory accident, and the other died in a motor scooter accident. Three others had undergone operation. In one of these three cases, first a colostomy and later an ileostomy were performed. The patient was thoroughly unhappy. Another had undergone ileostomy and colectomy and was getting along reasonably well. A third died promptly after ileostomy from what was said to be hepatic failure. One was of the uncooperative variety. Seventeen were greatly improved. One girl had remained well and had married. Fifteen reported their condition as fair and said they were getting along well, going to school and doing the things children of their age customarily do. Forty-six others reported their condition with such words as "entirely well," "excellent," "very good" and "good."

We have, then, a close follow-up on 126 of the 139 children as of January 1, 1955, and it is reasonable to suppose that we shall hear from some of the 13 who have not yet replied to the follow-up letter. However, an analysis of the present status of 91 per cent of these children should give us a good idea about the progress of the group as a whole.

A Program of Management

On the basis of our observation of these children over a period of years, it has become obvious that a well-ordered program of management is of extreme importance if their intestinal condition is to come under control.

When adults with advanced ulcerative colitis are past the toxic phase of the colitis one can reason with them and obtain cooperation in their program of rest, diet, avoidance of upper respiratory infections, and many phases of their activity designed to check a chronic debilitating disease. Younger children must be treated in a much more objective manner, and their program needs to be monitored constantly by an adult.

We have found that it is well to start a program of education and management of children who have ulcerative colitis in the hospital where they can be taught something about their problem and educated in the diet, and where a study can be made of the necessary medications, the patient's tolerance to them and the dosage required. Also, in the hospital various observations and study of these children, such as their relationships to the parents and other children in the family, can be better conducted, and those interested in the psyche of these children can better conduct their studies. It is, therefore, usually necessary to keep these children under observation for several weeks, and during this time a discussion of a plan for their future living is carried out. A dietary program is established and the dosage of medicines is ascertained.

It has been found that these children, just as adults, do best on a diet high in protein, high in vitamins, high in calories, and low in residue, but to attain the best attitudes toward such a diet and to get the child to partake of it in a satisfactory manner are frequently large problems; if for no other reason than to educate the child in this, the hospital program becomes valuable.

For active control of the intestinal infection, three important measures have emerged from our many efforts. These are blood transfusions, the proper use of antibiotics and the administration of salicylazosulfapyridine (azopyrin, azulfidine). During the acute or fulminating phase of this disease, the establishment of proper fluid balance is of the greatest importance. The study of levels of potassium and other electrolytes is of great value. Any imbalance should be corrected.

Blood transfusions are probably among our most valuable assets. This is well attested by the fact that 67 of these 139 children received blood transfusions, two of them having had 22 transfusions each, ranging from 200 to 500 cc. of blood. In most instances it is well to keep the transfusions to about 250 cc. or sometimes even less.

The antibiotics of choice in the seriously ill patient have been oxytetracycline (TERRAMYCIN®) and chloramphenicol (CHLOROMYCETIN®). Fortunately, a relatively small number of these youngsters are afflicted with the fulminating type of this illness. Just as in adults, the drug which has been found to be of greatest value in the average child with

ulcerative colitis is salicylazosulfapyridine (azopyrin, azulfidine). The dose is proportionately smaller than in adults and the average dose is 0.5 gm. in the child from 6 to 10 years of age. Extra vitamins, particularly of the B complex, have been helpful in improving the child's appetite and his sense of well-being. The use of the hormones cortisone and corticotropin has not found favor in the management of this disease in children. The rest of the program has been so much more valuable and such complications as arthritis and pyoderma gangraenosum are so infrequent that it is indeed a rare case in which these hormones have even a questionable indication.

We come to the problem of surgery. Up to now, we have records of operations in seven of these children, which is an incidence of just 5 per cent. This stresses the desire to avoid surgery in these youngsters if at all possible. However, there are some unpleasant complications in which surgery becomes the treatment of choice. In two of these children carcinoma developed. This is quite obviously an increase in the ratio of carcinoma in children of this age over that found in normal children. One of these patients was 17 years of age and the other was 18 years of age at the time of the operation. A third patient was 23 years of age at the time when operation was performed but she belonged to this juvenile group at the time her colitis began. One of these patients underwent operation because of extensive fistulas.

If the time comes for surgery in these children, the indications are for ileostomy and colectomy, just as in adults. This imposes an unusual handicap on the child who has to become accustomed to living with an ileac stoma. Consequently it is well to give him or her the best type of ileac stoma possible. Our experience with a large group of adults indicates that the skin-grafted ileac stoma has many qualities superior to other conventional types. The skin can be kept clean. The ileac contents are readily controlled and can be carried into almost any container, and the child finds it much easier to take care of such a stoma than of another type.

As in adults, it is undoubtedly best to limit surgery to the several complications, including extensive secondary polyposis, carcinoma, extensive secondary fistulas, and occasionally stricture and perforation. Rectal strictures are not necessarily indications for surgery. We have seen numerous cases in which strictures of the rectum developed which we have been able to dilate digitally, and we have found that, as the disease comes under control and is healed, the rectal lumen may return to adequate caliber and in a number of cases almost to normalcy.

It becomes evident, then, that ulcerative colitis in children is not greatly unlike that in adults. Children vary from adults in the physician's approach to this illness, and only in this sense can one discuss the condition in terms different from ulcerative colitis in adults.

REFERENCES

1. Helmholz, H. F.: Chronic ulcerative colitis in childhood. Am. J. Dis. Child. 26:418-430 (November) 1923.
2. Jackman, R. J., Bargen, J. A. and Helmholz, H. F.: Life histories of ninety-five children with chronic ulcerative colitis: A statistical study based on comparison with a whole group of eight hundred and seventy-one patients. Am. J. Dis. Child. 59:459-467 (March) 1940.
3. Benson, R. E. and Bargen, J. A.: Chronic ulcerative colitis as a cause of retarded sexual and somatic development. Gastroenterology 1:147-159 (February) 1943.

Drug Allergies

CHAUNCEY D. LEAKE*

The University of Texas Medical Branch, Galveston

C. D. LEAKE

THERE seems to be an unconscious conspiracy of silence in regard to reporting untoward drug reactions. Occasional case reports in some of the major medical society journals describe unsatisfactory responses to new drugs, but there is almost nothing on toxic reactions to well-known and commonly used drugs. Occasionally, reports to health authorities on drug toxicity are summarized, but these merely show the extraordinary extent of toxic drug reaction without much concern over what may be at stake.

Drug manufacturers have well assumed full responsibility for introducing new drugs into clinical use with careful control of toxic and allergic symptoms. Naturally, drug manufacturers want their new drugs to go over well. Nevertheless, they are wise, as experience abundantly shows, in calling attention repeatedly to the possibility of unfavorable reactions, when these are reported.

This increasing sense of responsibility on the part of drug manufacturers imposes additional obligations on physicians to report clearly and fully all cases of unsatisfactory responses to drugs. These may be reported directly to the drug manufacturers in the case of new drugs. When old and commonly used drugs are involved, the reports might be made through state medical journals. It might be wise indeed for state medical societies to issue annual reports on drug toxicity, through standing committees appointed to deal with this continuing problem.

Fortunately the Food and Drug Administration of the Department of Health continually reviews the question of drug toxicity. The regulations of the Food and Drug Administration with regard to the introduction of new

*Executive Director, The University of Texas—Medical Branch; Professor of Pharmacology, University of Texas School of Medicine, Galveston, Texas.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

drugs are wisely devised and ably administered. While opinions may differ from time to time among drug manufacturers, pharmacologists, and officials of the Food and Drug Administration on technical matters regarding new drugs, in general all may be well satisfied with the protection given by the Food and Drug Administration in so rigorously controlling the introduction, use and promotion of new chemical agents in medicine.

Outstanding for nearly half a century has been the work of the Council on Pharmacy and Chemistry of the American Medical Association in furnishing full information on the potential dangers of new drugs. The reports of the Council are also detailed and helpful with regard to toxic reactions from well-known and widely used drugs. Unfortunately, not enough physicians are acquainted with the work of the Council on Pharmacy and Chemistry to keep abreast of the reports published regularly in the *Journal of the American Medical Association*. It would be worthwhile for every practicing physician to keep a file of these reports for ready reference.

Allergic Reactions

Before discussing specific symptoms or management of drug allergy, it might be wise to consider what allergic reactions are in general, and also the types of chemicals to which allergy may develop.

Allergic manifestations to drugs may be classified in three ways: (1) those localized in special organs or tissues, examples of which are urticaria, hives, diarrhea, asthma, hay fever and agranulocytosis; (2) generalized severe and acute symptoms, as in anaphylactic shock, and (3) generalized mild and chronic reactions, of which fever may be considered typical.

London clinicians in the nineteenth century first clearly described the symptoms corresponding to what is now called allergy. In 1818 John Bostock described "summer catarrh," now known as hay fever. John Elliotson, famed for his studies in hypnotism, recognized pollen as the cause of hay fever in 1831. In 1860 Henry Salter gave the first clear clinical account of asthma. Liveing in 1873 realized that sick headache is related to hay fever.

French workers later developed modern concepts of allergy. Portier and Richet described anaphylactic shock in 1902. In 1903 Arthus reported the local tissue pathology of an allergic reaction. Pirquet noted serum sickness in 1905, and later he coined the term "allergy." Schloss first noted food allergy in 1912, and in 1914 Landsteiner analyzed drug allergy. The notion that fever might be considered a generalized mild form of allergy was implied by Barbour in 1921.

According to Barbour, contact with provocative proteins, and with certain drugs, causes water imbibition by cells, with congestion where the imbibition occurs and with hemoconcentration if the process is general. The localized congestion and swelling cause many of the local symptoms of allergy. However, if hemoconcentration occurs, not enough water may be available for loss by evaporation from lungs and skin. As the cooling mechanism is reduced, body temperature rises and fever is noted.

Meanwhile, the classic pharmacologic study in 1910 of Dale and Laidlow on histamine showed that this chemical is a natural component of living cells and is released when cells are injured, as in an allergic reaction. Dragstedt and Gebaur furnished proof of this theory. Allergic symptoms result from release of histamine, heparin and possibly choline from sensitized cells due to changes in permeability in the antigen-antibody reaction. It is not clear how the change occurs.

Tissue culture studies of human nasal mucosa reported by Rose, Pomerat and Danes show directly how histamine, or antigens to which the mucosa is sensitive, cause (1) breaking of lipoprotein granules in the cells; (2) gelation of cytoplasm, and (3) slowing of metachondral and ciliary movements. The tendency to gel under the influence of the antigen suggests the water imbibition and swelling of the cell, as implied by Barbour.

Certain aspects of cellular stability were shown by Wolbach to be dependent on ascorbic acid and vitamin A. Reid indicated the importance of carotenoids, calcium and hyalu-

ronic acid in maintaining intercellular cement and cell membrane stability. Chase, White and Dougherty demonstrated that the adrenocortical steroids are also implicated in the maintenance of healthy cellular colloidal stability, and clinical experience has abundantly confirmed the value of cortisone in allergy.

There are, then, a multiplicity of factors involved in the complex physical-chemical reaction in allergy. The inherited variations of metabolic and enzyme patterns of cells and cellular membranes in a particular individual are important. Vitamin deficiencies open the way for allergic reactions. Adrenocortical steroids seem to be essential for maintaining optimal sodium-potassium balance within cells and in relation to cell membranes, and for preserving the integrity of enzyme systems necessary for cellular stability. Relative lack of the vitamins or hormones involved may make cells more vulnerable to injury by contact with provocative allergens or allergy-producing drugs, or may make possible more immediate release of histamine than ordinarily occurs in healthy cells. When an individual is not in a healthy balance, it may also be that the usual histamine release in the allergic reaction cannot be handled in normal fashion.

The immediate allergic reaction results from interaction of a complex molecule comprising the allergen, which in some instances may be a combination of a relatively simple drug with an amino acid, with some particular molecule of the cell surface in such a way as to disturb the cell surface, release histamine, and induce water imbibition by the cell. This reaction occurs only to those protein complexes to which the cell surface has become "sensitized." So far there is merely speculation regarding the details of the phenomenon of sensitization.

All investigators agree that the allergic reaction results in histamine release. The biologic effects of histamine are thoroughly reproducible, as summarized by Selle. It is presumed that histamine comes from histidine or from various unstable protein combinations. Its formation may be blocked under ordinary circumstances by the balanced enzyme systems involving histaminase and combination with various proteins. In allergy, however, these systems may not be operative, and enough histamine accumulates to exert its characteristic toxic action. If the action of histamine can be blocked by a competitive compound, histamine effects do not appear. This apparently happens in the case of antihistaminic drugs. This may also happen in desensitization, when immune bodies may be formed from globulin in the reticuloendothelial cells which, as Burnet has shown, may block allergens from reacting with the cell surfaces.

Allergy then follows contact with or ingestion of foreign colloid complexes to which sensitization of the body cells has occurred. Such sensitization may result from contact with certain drugs. An obvious method of handling the allergy is to find the particular agent to which the individual is sensitive and then to prevent contact with it. This is relatively simple in the case of drugs, since the allergic reaction is so definitely associated with the ingestion of the particular drug to which the person may have become sensitized. As Burnet suggests, sensitization may follow stripping of protein molecules from cell surfaces by contact with the sensitizing agent, preventing antibody formation.

Depending on local conditions of vitamin, hormone and mineral balance, together with local factors of circulation and general metabolic stability, the allergic picture as expressed locally depends on the character of tissue involved. If it is skin, itching, rashes, wheals or hives may occur. In the eyes and nose it will be expressed as hay fever, and in the throat as coughing and congestion. If it is in the bronchi, it will result in asthma due to swelling of bronchial mucosa and musculature. If the allergic reaction occurs in the brain, the symptom may be headache. If it is in the gastrointestinal tract, there may be nausea, vomiting, cramps, colic and diarrhea. Allergic reactions may cause spasm and pain in the urinary tract, and similar symptoms in the biliary tract. There is reason to suspect that many types of visceral pain may be referable to localized allergic swellings and re-

actions. If the allergic condition occurs in bone marrow, agranulocytosis or thrombocytopenia may result. The localized expressions of allergy are therefore manifold. A more generalized reaction will result in fever. Drugs of various types may produce one or more of these various localized and generalized responses.

Chase emphasized that local irritation increases the incidence of sensitization. Carr suggested that known sensitizing agents should not be used locally when they can be given equally well parenterally, especially when attempting to treat a dermatitis. Wide clinical experience with the sulfonamide drugs and with penicillin provides the background for such recommendations.

In atopic dermatitis, as Pillsbury has shown, many etiologic factors are involved. These include contact with irritating or sensitizing chemicals as well as latent virus infections, metabolic conditions, sweat retention, and powerful psychologic factors.

Allergic tendencies may be reduced by an adequate protein intake, and by maintaining a satisfactory balance of steroid hormones and of the general vitamin complex. Psychogenic factors such as occur in anxiety or emotional stress may be involved in allergy and may be concerned with various phases of Selye's "alarm reaction." Emotional stress may interfere with the action of adrenocortical hormones, thus predisposing to allergic reaction when contact occurs with provocative molecules. Psychotherapy thus may be very useful in allergy management.

Sensitizing Drugs

Landsteiner showed that any chemical having a carboxyl, amino or hydroxyl group may combine in its metabolism in the body with various amino acids, thus forming a complex to which cellular sensitization may occur. Drugs of this type are many. They include many of the antibiotics, the sulfonamide compounds, many organic arsenical agents, many hormone preparations, and all sorts of aromatic amino, phenolic and carboxylic compounds. Similar reactions, especially involving the skin and perhaps representing some sort of allergic response, may also occur to such relatively simple inorganic compounds as the iodides and bromides. The barbitals, aspirin, the salicylates and their many derivatives, local anesthetics, and all types of analgesics may produce allergic responses.

In general, about 5 per cent of individuals have some allergic reaction to commonly used drugs. It is not possible to tell in advance where the allergy may appear, or in which patient. It is always wise for the alert clinician to ask patients about their possible sensitivity to various commonly used drugs. This may help avert trouble.

It is customary to classify toxic effects of drugs into two groups: (1) those due to overdosage and (2) those due to abnormal reactions. The latter sometimes are referred to as "idiosyncrasies." This is an unsatisfactory term. It is also not quite correct to refer to the latter as "drug hypersensitivity." Allergic reaction to drugs is definitely unusual and abnormal. It is not to be expected, and occurs only in about 5 per cent of individuals who receive commonly used drugs.

As Clark so well showed, the range of individual dosage varies widely, even on the basis of mass of drug in relation to mass of living tissue. Some persons are affected relatively slightly by the same dosage which in other individuals may produce marked effects. Some patients show signs of overdosage from very small amounts of certain drugs. Such persons may be called "hypersensitive." This term relates to the development of symptoms identical to those which might occur in any case in which a large enough dose of the drug in question is given.

Characteristically, drug allergies do not appear following the first administration of the drug, but become manifest only after sensitization has occurred. Sensitization may be so marked that use of such drugs as penicillin, the sulfonamide compounds, antithyroid agents and TRIDIONE® may be contraindicated. On the other hand, such drugs as epinephrine, caffeine, cascara sagrada and the general inhalation anesthetic agents have never been shown to cause sensitization. Contrariwise, such a chemical as phenylethylhydan-

toin, used in treating chorea, produces signs of sensitization in over 90 per cent of patients.

Specific types of allergic reaction to certain drugs are hepatitis to cinchophen, arsphenamine or sulfonamides; agranulocytosis to aminopyrine, sulfonamide drugs, arsphenamine, thiouracil, Tridione and gold salts; thrombocytopenia to certain urea depressants such as SEDORMID®.

According to Robson, allergic drug reactions are characterized by (1) reactions which differ from the ordinary pharmacologic effects of the drug; (2) allergic symptoms reproduced on subsequent administration of the drug, sometimes of small doses, after an incubation period of four days to two weeks after first exposure; (3) symptoms typical of allergic conditions; (4) positive reactions to skin patch tests in some instances; (5) no demonstrable serum antibodies, unless they are present in lymphocytes; (6) a reaction usually specific for one drug or closely related chemicals; (7) histologic effects similar to those found in ordinary allergic conditions, and (8) local and systemic symptoms similar to histamine responses.

Skin eruption is the most frequent manifestation of drug allergy. All types of skin lesions may result, and a sensitizing drug may produce different responses in different individuals. The commonest skin reactions to drugs are the urticarial and maculopapular conditions caused by ingestion of penicillin, streptomycin, quinine, sulfonamide compounds, salicylates and barbiturates. Such erythemas as occur in rheumatic or tuberculous conditions may follow administration of bromides or sulfathiazole. Contact dermatitis sometimes follows application of antibiotic or sulfonamide preparations to the skin.

Marked fever has been reported following use of such drugs as iodine, sulfonamide compounds, antibiotics and thiouracil. Deaths have occurred from use of sulfonamide compounds, and certainly many near deaths from penicillin. In the case of the sulfonamide compounds, cross sensitization has been reported, although allergic responses are greater in connection with the original sensitizing agent. Many alkaloids may cause allergic effects, although such responses are not frequent. Atropine and its derivatives, however, quite often give allergic reactions when applied locally to the eyes.

The extraordinary general interest in "tranquilizing agents," such as chlorpromazine, the Rauwolfia alkaloids and 2-piperidyl dibenzhydrol, suggest that possible allergic reaction to them should be considered. Allergic skin reactions to chlorpromazine are estimated in some series as occurring in 10 per cent of the patients to whom the drug is given. The drug also has reportedly caused hay fever, nausea, spiked fever reactions and even parkinsonian symptoms. Photosensitivity may be a factor in skin reactions to this agent. Cohen and Archer reported the possibility of occasional allergic reaction in the liver resulting in jaundice; in two of their five cases in which signs of obstructive jaundice occurred, skin reactions also were present.

The chemical composition of 2-piperidyl dibenzhydrol suggests that allergic reactions may occur to this compound, in accordance with the Landsteiner theory. Although the hydroxyl and carboxyl groups of reserpine are muzzled, it is possible that with metabolic change in the body these reactive radicals in the molecule may become available for combination with amino acids. There are thus produced circumstances favorable to the development of allergic symptoms, as Landsteiner proposed.

Lehr demonstrated a relationship between size of dosage and frequency of sensitization. Fewer allergic side effects are noted with small doses of various sensitizing drugs than with large doses. Sensitization to drugs may persist for many years. Although Hopkins and Lawrence reported evidence that sensitization to penicillin is relatively temporary, subsequent reports indicate that in some cases sensitization may last a relatively long period. Park reported successful desensitization to sulfonamide compounds. In general, however, desensitization to drugs has not been successfully accomplished.

The mechanism of drug sensitivity has been most thoroughly studied by Landsteiner and associates. This work was well summarized by

Robson. Harvey emphasized that sensitization reactions to drugs appear to be "all or none" events which, once developed, are not reversed by withdrawing the offending drug. Accordingly, drugs known to be capable of producing sensitization should not be used in repeated courses of therapy. The risk in their use should always be weighed against the hazard of the disease in the particular case in which they may be indicated.

Allergy to Antibiotics

Allergic reactions to antibiotics occur frequently, whether the drugs are administered parenterally or locally. Penicillin seems to be the most serious offender, probably because of its wide use. Reactions to penicillin are extremely common in the skin. They may include exfoliative dermatitis, even involving the palms of the hands. Very often the reaction is expressed as hives and urticaria. This skin allergy to penicillin may last for a long time. It seems to depend on the rate at which penicillin is removed from the body. When allergy to penicillin occurs, the rate of destruction or removal of the drug from the body seems to be prolonged. Skin reactions to penicillin frequently occur in cases of persons who are particularly alert, who have some anxiety or emotional stress or are tired or overworked.

Acute anaphylactic reactions to penicillin are becoming increasingly common. These may result from parenteral administration of penicillin to individuals who are generally sensitized to the drug, and occur regardless of the form in which it is prepared. The acute reaction is sudden and severe and may require emergency measures to save life. It may be wise for physicians to carry sterile solutions of epinephrine for prompt administration when such an acute emergency reaction to penicillin occurs.

There may be danger in delaying the excretion of penicillin in its initial use in a patient. This delay may give further opportunity for sensitization. Certainly *p*-aminohippuric acid and carinamide should be used with caution in prolonging penicillin action. Oral administration of penicillin and penicillin preparations may well be preferred to their use parenterally, to reduce the tendency to sensitization or to allergic reaction.

Local irritation and other unsatisfactory aspects of administering penicillin have been reduced by increased purity of product; however, it does not seem that the improved preparations are any better from the standpoint of allergic reaction. Penicillin contains a carboxyl group which, even if muzzled in various penicillin derivatives, may still appear on the hydrolysis which probably occurs when muzzled compounds are metabolized. This free carboxyl group certainly fits into the Landsteiner picture of drug allergy.

Molitor and associates made exhaustive studies of the pharmacology and toxicology of streptomycin and showed clearly that with improved purity, toxic reactions are less. In general, human beings seem to be more sensitive to streptomycin than experimental animals and show a variety of untoward effects, even to the pure product. These range from small falls in blood pressure to respiratory and neurotropic effects. The latter seem to be localized in the eighth nerve, with vestibular disturbance and some interference with hearing ability.

Eosinophilia frequently appears following administration of streptomycin, and this eosinophilia can be relieved by antihistaminics. This would seem to be evidence of an allergic response to streptomycin. Indeed, direct allergic symptoms occur after streptomycin is administered, and these usually involve the skin. Rashes, maculopapular eruptions and exfoliative dermatitis are described. Skin reactions occur in individuals who handle streptomycin, and positive skin tests indicate the existence of streptomycin sensitivity. There may also be joint swelling and pain, which could be explained on an allergic basis.

Streptomycin contains free phenolic groups which might react in accordance with the Landsteiner hypothesis to produce compounds in the body to which sensitization may occur. Dihydrostreptomycin seems to be somewhat freer from neurotoxicity than streptomycin, and also freer from allergic response. Dihydrostreptomycin is therefore the drug of choice when streptomycin therapy is indicated.

AUREOMYCIN® causes considerable gastrointestinal disturbance, including nausea, vomiting and diarrhea. These symptoms usually are noted only after repeated administration. They may be due to impurities or to allergic sensitivity of the intestinal mucosa. Parenteral administration of Aureomycin is irritating.

Chloramphenicol contains free hydroxyl groups which can react in the manner proposed by the Landsteiner theory to produce allergic effects. This antibiotic is quite toxic, and its administration to persons with typhoid fever and rickettsial diseases requires care. Its toxicity, however, does not seem to be related to its possible allergic activity.

The toxicology of antibiotics was well reviewed by Molitor and Graessle in 1950. Since then, however, much more information has accumulated regarding allergic reactions to various antibiotics. Even those of broad activity and low toxicity, as estimated experimentally, may show allergic effects, usually referable to the skin.

Certainly on the basis of existing evidence, antibiotics should be used with caution. They should be employed when definitely indicated, and not administered routinely on cases of sore throat or mild infection. Under circumstances of routine administration, sensitization to the antibiotics can occur and may result in serious consequences later when a real infection strikes and the full force of an appropriate antibiotic is desired.

Management of Drug Allergies

It probably is very wise clinically to stop the administration of any drugs whenever symptoms appear that may raise the suspicion of allergic reactions. Certainly the most effective way of reducing allergic reaction to any drug is to stop its administration. However, acute allergic reactions may occur, as in penicillin-sensitive individuals. Here epinephrine is clearly indicated and should be administered promptly and parenterally in sufficient dosage to produce the characteristic sparing action of epinephrine in anaphylactic shock. In acute and severe anaphylactic shock, 1 cc. of a 1 to 10,000 concentration of epinephrine hydrochloride may be given intravenously. This may then be supplemented by subcutaneous injection as symptoms warrant.

In general the management of drug allergy is symptomatic. Local irritation should be reduced to a minimum, whether on mucous membranes or skin. Steps should be taken to restore vitamin, hormone and mineral balance. Ascorbic acid, carotene and cortisone in general are indicated. These help to pack cells together and to develop the usual healthy cellular fluid and electrolyte balance. Whatever is possible should be done to hasten the elimination of the allergy-causing drug. Antihistaminics are of relatively little value after allergic symptoms appear.

Cortisone is widely recommended for treatment of various allergic reactions. It is useful in drug allergy. It has been widely employed in allergic responses to penicillin. Allergy to penicillin is claimed to be of the delayed serum sickness type, with chief manifestations in the skin. The characteristic urticaria clears after the oral administration of a single large dose of cortisone. Usually, however, effective therapy requires an initial dose of 100 mg. followed by 50 mg. every four hours for six to eight doses, and then every six hours for an additional day. Cortisone therapy must be carefully watched. Depending on the rate of removal of penicillin from the body, the urticaria may not reappear after cessation of cortisone treatment. Corticotropin is quite as effective as cortisone in relieving the various manifestations of penicillin allergy, but relief is less rapid.

Serum sickness may be considered to be a form of drug allergy. It is relieved rapidly by administration of cortisone in doses of 100 mg. orally every four hours, followed by 50 mg. every four to six hours for an additional day. Corticotropin itself is a protein complex and can produce allergic effects. There may also be allergic reactions to insulin.

Cortisone also has proved helpful in treating agranulocytosis following the administration of a sulfonamide drug or other bone marrow-depressing compounds. Similarly, cortisone relieves exfoliative dermatitis resulting from arsenical or antibiotic treatment. It is not clear whether or not cortisone is helpful

in cases of rash caused by bromides or iodides.

In all cases of skin eruption resulting from drug therapy, cortisone seems to be effective. These include angioneurotic edema, contact dermatitis, atopic dermatitis, exfoliative dermatitis and erythema multiforme. For the latter, cortisone is the only effective therapy known. In all these conditions cortisone therapy is clearly indicated in severe cases. Cortisone is not recommended for treatment of mild atopic dermatitis. Hydrocortisone ointment is preferable in localized contact dermatitis.

Summary

A general consideration of allergic reactions indicates the extreme complexity of the process. In accordance with the evidence provided by Landsteiner, drugs may cause allergic reactions if they contain reactive groups capable of combination with amino acids or protein complexes. Such drugs may produce allergic manifestations localized in special organs or tissues, generalized acute and severe anaphylactic shock, or mild chronic reaction of which the chief symptom may be fever. Histamine release is involved in the allergic reaction, as are immunity mechanisms.

Many types of drugs may cause allergy. Of particular interest are allergic reactions resulting from antibiotics. Skin manifestations are certainly the most common consequence of drug allergy.

Drug allergy is most satisfactorily managed by withdrawing the drug promptly when allergic symptoms appear and administering cortisone, as well as cellular-stabilizing agents such as ascorbic acid.

Physicians are urged to record allergic reactions to the drugs that they may use. It is also suggested that state medical societies maintain drug toxicity committees to collect and analyze reports on drug toxicity with particular reference to allergic reactions. Such reports may give helpful information regarding the cause, character and management of drug allergy.

REFERENCES

1. Arthus, N. M.: Injections Répetées de Serum de Cheval Chez le Lapin. C. R. Soc. Biol. 55:817-820, 1903.
2. Barbour, H. G.: The heat-regulating mechanism of the body. Physiol. Rev. 1:295-326, 1921.
3. Bostock, J.: Case of periodical affection of the eyes and chest. Med. Chir. Tr., London 10:161-165, 1819; 14:437-446, 1818.
4. Burnet, F. M.: The basis of allergic diseases. M. J. Australia 1:29-35 (January 10) 1948.
5. Cahr, E. A.: Allergy to drugs. New England J. Med. 245:892, 1951.
6. Chambers, R. and Swkifach, B. W.: Intercellular cement and capillary permeability. Physiol. Rev. 27:436-463, 1947.
7. Chase, J. H., White, A. and Dougherty, T. F.: Enhancement of circulating antibody concentration by adrenal cortical hormones. J. Immunol. 52:101-112, 1946.
8. Clark, A. J.: Variations in the individual response to drugs. Edinburgh M. J. 42:1-16 (January) 1935.
9. ——: General Pharmacology. Berlin, Springer, 1937, vol. 4, 228 pp.
10. Cohen, I. M. and Archer, J. D.: A study of liver function and hepatic complications in patients receiving chlorpromazine. (In press.)
11. Dale, H. H. and Laidlow, P. P.: The physiological action of B-iminazolyle-thylamine. J. Physiol. 41:318-344, 1910.
12. Dragstedt, C. A.: Anaphylaxis. Physiol. Rev. 21:563-587, 1941.
13. Elliotson, J.: Hay fever. London, M. Gaz. 8:411-416, 1831.
14. Harvey, A. M.: Allergic reactions to therapeutic agents. In Lukens, F. D. W. (ed.): Medical Uses of Cortisone. New York, The Blakiston Company, Inc., 1954, pp. 348-356.
15. Heidelberger, M.: Immuno-chemistry of antigens and antibodies. In Cooke, R. A.: Allergy in Theory and Practice. Philadelphia, W. B. Saunders Company, 1947, pp. 81-89.
16. Hopkins, J. D and Lawrence, H.: Sensitization to penicillin. J. Allergy 18:251-261, 1947.
17. Landsteiner, K.: The Specificity of Serological Reactions. Springfield, Illinois, Charles C Thomas, 1936, 178 pp.
18. Leake, C. D.: A pharmacologic analysis of drugs used in allergy. Texas Rep. Biol. Med. 9:322-340, 1951.
19. Lehr, D.: Lowered incidence of sensitization through use of sulphonamide combinations. Brit. M. J. 2:543-548 (September 18) 1948.
20. Liveing, E.: On Megrim, Sick-Headache, and Some Allied Disorders. London, J. Churchill, 1873.
21. Meyer, K.: Biological significance of hyaluronic acid and hyaluronidase. Physiol. Rev. 27:335-359, 1947.
22. Molitor, Hans and Graessle, O. E.: Pharmacology and toxicology of antibiotics. Pharmacol. Rev. 2:1-60, 1950.
23. Park, R. G.: Sulphonamide allergy. Brit. M. J. 1:781-782 (June 10) 1944; 2:816-817 (December 23) 1944.
24. Pillsbury, D. N. and Urbach, F.: Diseases affecting the skin. In Lukens, F. D. W. (ed.): Medical Uses of Cortisone. New York, The Blakiston Company, Inc., 1954, pp. 357-386.
25. Pirquet, C. P. and Schick, B.: Die Serum-krankheiten. Wien, F. Deuticke, 1905; Klinische Studien uber Vakzination und Vakzinale Allergie. Wien, F. Deuticke, 1907.
26. Portier, P. P. and Richet, C. R.: De l'Action Anaphyloctique de Certains Venins. C. R. Soc. Biol. 54:170-172, 1902.
27. Reid, M. E.: Interrelations of calcium and ascorbic acid to all surfaces and intercellular substances. Physiol. Rev. 23:76-99, 1943.
28. Robson, J. M. and Keele, C. A.: Sensitization to drugs (drug allergy). In: Recent Advances in Pharmacology. Philadelphia, The Blakiston Company, 1950, chapter 4, pp. 87-98.
29. Rose, J. M., Pomerat, C. M. and Danes, B.: Tissue culture studies of ciliated nasal mucosa in man. Anat. Rec. 104:409-420, 1949.
30. Salter, H. H.: On Asthma: Its Pathology and Treatment. London, J. Churchill, 1860.
31. Schloss, O. M.: A case of allergy to common food. Am. J. Dis. Child. 3:341-362, 1912.
32. Selle, W. A.: Histamine: Its physiological, pharmacological and clinical significance. Texas Rep. Biol. Med. 4:138-244, 1946.
33. Selye, Hans: Stress. Montreal, Acta, Inc., 1950, 822 pp.
34. Sevag, M. G.: Immuno-Catalysis. Springfield, Illinois, Charles C Thomas, 1945.
35. Sherman, W. B.: Drug allergy. Am. J. Med. 3:586, 1947.
36. Wolbach, S. B. and Bessey, D. A.: Tissue changes in vitamin deficiencies. Physiol. Rev. 22:233-289, 1942.
37. Wolbach, S. B. and Howe, P. R.: Intercellular substances in experimental scorbutus. Arch. Path. 1:1-24, 1926.

Early Ambulation Following Primary Inguinal Hernioplasty

LOUIS T. PALUMBO*

Veterans Administration Hospital, Des Moines

THE beneficial effects of early ambulation during the postoperative period are not widely known. This method of treatment is not new, for it was reported by Ries[1] in 1899. Its use has been stimulated by the publication of a relevant article in 1941 by Leithauser and Bergo.[2]

LOUIS T. PALUMBO

It is inconceivable that it has taken about 50 years for the surgical groups in this country to institute this program. However, it still is not used generally throughout the country. This is due to many reasons, one of which is a reluctance on the part of many physicians and surgeons to institute ambulation early, particularly in cases in which a primary inguinal hernioplasty has been performed, because of the misconception that such a program has a deleterious effect on wound healing and, therefore, increases the chance for a recurrence of the hernia. Many are of the opinion that the lines of stress and strain are peculiarly different in this area of the body as compared with those in adjoining areas of the upper part of the abdominal wall. Because of this, they rationalize that delayed healing of the wound would occur and thereby result in a poor repair, which would eventually lead to a recurrence. These concepts can be readily dispelled by a proper evaluation of the results as reported in the literature.[3-12]

According to Speir,[12] the wound-healing curve of Harvey and Howes shows that the tensile strength of healing wounds is lowest from the third to the fifth day after operation. Wound healing is not complete until the twelfth or fourteenth day. Prolonged rest in bed depresses the circulation in the area of the wound and thereby delays healing. All of these factors influence the strength of healed wounds.

On the other hand, early postoperative ambulation enhances wound healing, and, according to reports, has not increased the incidence of recurrence following primary inguinal hernioplasty.[3-11] Other benefits of such a program include a reduction in the incidence of complications which may occur in the gastrointestinal tract and on cardiovascular, pulmo-

*Department of Surgery, Veterans Administration Hospital, Des Moines, Iowa.

nary and peripheral vascular systems.[3-11]

Aside from the factors of safety and the reduction in the incidence of complications, it is important to point out the socio-economic factors of such a program. The more rapid rehabilitation of the patient is desirable, and it is also a great morale builder. The reduction in the period of hospitalization represents a great saving in medical costs both to the patient and to the hospital. It also provides for greater utilization of existing hospital beds.

It is important to recognize that nothing replaces a sound and basic surgical repair, particularly in cases of inguinal hernia. It is readily apparent to anyone who has studied the literature that there is a wide variation in the recurrence rates following a primary hernioplasty. The rate may range from a low of 1.1 per cent to a high of 36 per cent.[3,10] The higher rates are more frequent in the hands of the untrained and/or occasional operator. A sound basic anatomic repair should take priority over any method of postoperative management. On the assumption that the surgical repair has been sound, a program of early postoperative ambulation will result in an over-all favorable outcome.

Early ambulation in cases of inguinal hernia consists of getting the patient out of bed the day of the operation, or early the next day, and having him stand, walk and sit. These activities are increased daily and are carried out in conjunction with deep breathing and leg exercises, which are instituted immediately after the patient recovers from the anesthetic.

The same basic type of repair has been used in all those cases in which a primary inguinal hernioplasty has been performed by the author and his associates on adults during the past 15 years.[7,10] A careful follow-up study of a large series of cases in which inguinal hernioplasty was performed before the institution of early ambulation revealed that the recurrence rate was less than 2 per cent.

In order to compare the effects of early and late ambulation, Paul, Mighell and I[10] recently made a follow-up study of 1,236 consecutive cases in which a total of 1,375 inguinal hernioplasties was performed on male patients. The patients were followed for periods ranging from one to six years after operation. In 873 cases, ambulation was instituted on the first day; in the remaining 363 cases, it was instituted between the seventh and fourteenth day after operation. The complication rate was 5.7 per cent in the cases in which ambulation was instituted early and 19.4 per cent in the cases in which it was instituted late. The recurrence rate was about the same in both groups. It was 1.2 per cent in the group in which ambulation was instituted early and 1.3 per cent in the cases in which it was instituted late.

Summary

It is apparent that early ambulation is beneficial in effecting a marked decrease in the complication rate without increasing the recurrence rate in cases in which an inguinal hernioplasty is performed. The effect on the wound appears beneficial, too; in addition, the patient is more rapidly rehabilitated, his morale is better, and there is great economic saving to the patient, to industry and to the hospital. A more widespread adoption of an early ambulatory program in the care of the surgical patient appears warranted, since it is a sound anatomic and physiologic policy.

REFERENCES

1. Ries, E.: Some radical changes in after treatment of celiotomy cases. J.A.M.A. 33:454 (August 19) 1899.
2. Leithauser, D. J. and Bergo, H. L.: Early rising and ambulatory activity after operation; a means of preventing complications. Arch. Surg. 42:1086 (June) 1941.
3. Conkling, R. W.: Surgical treatment of inguinal hernia; review of literature. Surgical Staff Meetings, Veterans Administration Hospital, Des Moines, Iowa 3:1 (June 1) 1951.
4. Katz (Knight), I. A.: Early ambulation in management of surgical patient; review of literature. Surgical Staff Meetings, Veterans Administration Hospital, Des Moines, Iowa 4:1 (November 1) 1950.
5. Martin, D. J.: Active convalescence of hernial repairs. Brit. M. J. 2:531 (October 21) 1944.
6. Palumbo, L. T. and Paul, R. E.: Effects of early ambulation in primary inguinal hernioplasty. Am. Surgeon 18:1128 (November) 1952.
7. Palumbo, L. T., Paul, R. E. and Emery, F. B.: Results of primary inguinal hernioplasty. Arch. Surg. 64:384 (March) 1952.
8. Palumbo, L. T., Samberg, H. H., Paul, R. E., Katz (Knight), I. A. and Mazur, T. T.: Effects of early and late ambulation upon the surgical patient. Am. J. Surg. 85:544 (April) 1953.
9. Palumbo, L. T., Paul, R. E., Katz (Knight), I. A. and Mazur, T. T.: Effects of early postoperative ambulation. Postgrad. Med. 13:206 (March) 1953.
10. Palumbo, L. T., Paul, R. E. and Mighell, S. J.: Primary inguinal hernioplasty; study of 1,375 cases. S. Clin. North America 567 (April) 1954.
11. Powers, J. H.: Prompt postoperative activity after hernioplasty; its influence on incidence of complications and rate of recurrence. Arch. Surg. 59:601 (September) 1949.
12. Speir, E. B.: Symposium on use and abuse of bed-rest; surgery. West. J. Surg. 54:328 (August) 1946.

The Appreciation of Flavors

EDWARD C. CLARK* AND HENRY W. DODGE, JR.**

Mayo Clinic and Mayo Foundation, Rochester, Minnesota

WE perceive taste in the mouth when we squeeze it out by chewing food, just as if someone were to grasp a sponge full of water in his hand and begin to squeeze it dry. Next, all that we squeeze out is diffused through the pores of the palate and the winding channels of the spongy tongue. When the trickling particles of savour are smooth, they affect the palate pleasantly and pleasantly tickle all the moist regions of the tongue in their circuitous flow. Others (unpleasant flavors) in proportion as their shape is rougher, tend more to prick and tear the organs of sense by their entry."

In these words Lucretius[1] some 50 years before the birth of Christ proposed one of the first theories of flavor. Now, 2000 years later, one is forced to admit that surprisingly little advance beyond the theories of Lucretius has been made, and that much about man's ability to appreciate flavor remains unstudied and unexplained.

EDWARD C. CLARK

HENRY W. DODGE, JR.

With the pioneer studies of Brillat-Savarin[2] in 1825, Kneeland[3] in 1851 and Ogle[4] in 1870, considerable data which have been collected lead to the assumption that the flavor of substances is largely, if not entirely, dependent on olfaction. Best and Taylor[5] have pointed out that blocking of the nasal passages by an infection of the upper part of the respiratory tract seems to blunt the appreciation

*Section of Neurology, Mayo Clinic, and Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota.

**Section of Neurologic Surgery, Mayo Clinic, and Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minnesota.

of taste, and it may be then impossible to distinguish between the taste of an apple and that of a pear, or to distingush between a potato and a turnip. Moncrieff[6] has said that "people suffering from loss of smell also lose what they call their 'sense of taste,' but which is really their odor component of the flavor."

The concept that man's ability to appreciate and distinguish flavors depends largely on olfaction apparently has often been assumed in the past to apply to all persons seemingly without exception. When a patient reports that he has lost his sense of smell, but that his ability to distinguish between foods and to enjoy their flavor is maintained, the clinician may assume that the patient is mistaken about the defect in his olfactory apparatus and can actually experience odors, at least by way of his nasopharynx. The pertinent literature on the subject of the appreciation of flavor contains only a few papers that would contradict this opinion.[7-9]

Thus, some conflict of opinion exists as to the importance of olfaction in the identification and appreciation of flavors. Actually, many of the studies made so far have been rather incomplete. We have not been able to discover any cases cited in which the patient's olfactory nerves were proved to have been destroyed. Rather, it was assumed by the examiners that the olfactory nerves were not functioning, because the patients were, or said they were, unable to detect test odors. Apparently few of the authors of reports in the literature carefully examined the mouths of the patients they described, to determine the intactness of the somesthetic sensations of the buccal cavity.

Börnstein[10] maintained that under biologic conditions all gustatory stimuli act at the same time on the organs of touch, pressure and temperature. He also maintained that tactile and gustatory perception may merge to build an intersensory complex, which cannot be analyzed into its components. The use of lye as a test substance seems to produce an alkaline taste; however, the sensation produced apparently is composed of gustatory, olfactory, pain, temperature and touch modalities. Crocker[11] declared that: "No less than three distinct senses may be engaged in the perception of any particular flavor; the sense of tongue taste, the sense of smell, and the sense of feeling."

Over a period of years, we have noted a certain number of patients who have undergone intracranial operative procedures which may well have destroyed their olfactory nerves. Several of these patients, however, have continued to enjoy their food, although they have complained of their inability to smell odors of any kind. This interesting observation poses a question as to the importance of olfaction in the appreciation of flavor in different persons.

Recently, the opportunity arose for careful and detailed examination of two patients who had suffered destruction of the olfactory nerves by meningiomas of the olfactory groove as demonstrated at the time of operation. One of these patients[12] could name and appreciate the flavor of many test foods. For example, she could identify raw and cooked samples of apple, potato and pear. Without being asked, she correctly identified the raw apple as being of the Delicious variety.

The other patient appeared to have lost a considerable part of her appreciation of flavor, and could identify only a few of the foods placed in her mouth. In both cases, examination of the structures in the patients' buccal cavities did not reveal any detectable loss of taste or other sensations. Both patients were, of course, anosmic.

When one attempts to list and analyze the various factors that may combine to produce the composite of sensations identified by man as "flavor," certain things become apparent. As is generally agreed, olfaction and taste (ability to appreciate sweet, salty, sour and bitter sensations) are important. However, the role played by the other end organs in the buccal cavity, nasopharynx and adjacent structures cannot be ignored.

Pain, for example, enters into the appreciation of the flavor of food by warning of noxious substances and by helping to create the burning or biting sensation felt when certain spiced foods are eaten. The temperature of food is important in developing a desirable

flavor, from the standpoint of both olfaction and oral sensation. The ability of the structures of the mouth to appreciate the wetness or dryness of the substance being eaten enters prominently into the over-all appreciation of flavor, as also may, at times, vibration and other sensations by way of the teeth. Superficial touch, deep-pressure sensation, proprioceptive impulses from the tongue and muscles of mastication, two-point discrimination and stereognosis all play important roles in determining the consistency, texture, weight, size and shape of the substance eaten.

Other factors that are of considerable importance in the over-all enjoyment of flavor are vision, hearing and the psychologic orientation of the person at the time of eating.

Certainly, the color and general appearance of the food one is about to eat prepare him for the flavor he is going to experience. An example of the importance of color in this regard is the desire of the oleomargarine industry to color oleomargarine yellow, so that it will more closely resemble butter.

Hearing likewise enters into the enjoyment of foods, as evidenced by the advertisements of various well-known foods which are recommended because they "crackle" or are "crunchy" or "crispy," terms which have strong auditory components.

Finally, the psychologic orientation of the person when he eats a given food may influence his appreciation of that particular flavor, not only at that moment but for years to come. This psychologic factor is, of course, complex and involves many components. Among these, at least in part, are the aforementioned vision and hearing, as well as the memory the person has of the flavor experienced while eating the food on previous occasions and the setting in which the food is being eaten.

Thus, it would seem that all components of sensation experienced in the buccal cavity, nasopharynx and adjacent structures, vision, hearing and the psychologic state of the person at the moment, as well as olfaction, may combine to form a sensory composite which is identified as "flavor" at a cortical level in the brain. In many people, however, it would appear that olfaction is of primary importance, and that the loss of this sensation deprives the person of his ability to appreciate flavors. Others, however, can continue to identify and enjoy the flavor of many foods in spite of the absence of the sense of smell. Whether this difference in responses obtained is due to some unrecognized qualitative or quantitative individual variation in the sensory end organs of the buccal cavity and nasopharynx, or to central cerebral ramifications, or to varying psychologic factors, or to a combination of these, cannot be determined at this time. However, the difference in abilities among anosmic people to distinguish flavor would suggest the possibility, as yet unproved, that such persons might be trained to better identify and enjoy the flavor of food.

To quote an old Spanish proverb: "In matters of taste there can be no dispute." Everyone is his own judge.

REFERENCES

1. Lucretus: On the Nature of the Universe. (Translated by R. E. Latham.) London, Penguin Books, Ltd., 1951.
2. Brillat-Savarin, J. A.: The Physiology of Taste: Meditations on Transcendental Gastronomy. (Translated from the French by Charles Monselet.) New York, Liveright Publishing Corporation, 1948.
3. Kneeland: Case of an affection of the olfactory nerve, with total loss of smell and taste with remarks upon the probable identity of these two senses. Am. J. M. Sc. 21:41-46, 1851.
4. Ogle, William: Anosmia: Cases illustrating the physiology and pathology of the sense of smell. Tr. Roy. Med-Chir. Soc. 53:263-290, 1870.
5. Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice: A Text in Applied Physiology. Ed. 5, Baltimore, Williams & Wilkins Company, 1950, p. 1197.
6. Moncrieff, R. W.: The Chemical Senses. Ed. 2, London, Leonard Hill, Ltd., 1951, p. 437.
7. Hutchinson, J. C.: A remarkable case of change of complexion with loss of the sense of smell. Am. J. M. Sc. 23-24:146-148 (January) 1852.
8. Crosland, H. R., Goodman, M. and Hockett, A.: Anosmia and its effects upon taste perceptions. J. Exper. Psychol. 9:398-408 (October) 1926.
9. Leigh, A. D.: Defects of smell after head injury. Lancet 1:38-40 (January 9) 1943.
10. Börnstein, W. S.: Cortical representation of taste in man and monkey. I. Functional and anatomical relations of taste, olfaction, and somatic sensibility. Yale J. Biol. & Med. 12:719-736 (July) 1940.
11. Crocker, E. C.: Flavor. New York, McGraw-Hill Book Company, Inc., 1945.
12. Clark, E. C. and Dodge, H. W., Jr.: Effect of anosmia on the appreciation of flavor: Report of case. Unpublished data.

Diagnosis of Asymptomatic Malignant Disease

A REPORT OF SIX AND ONE-HALF YEARS' OPERATION OF THE CANCER DETECTION CENTER, UNIVERSITY OF MINNESOTA

CLAUDE R. HITCHCOCK* AND J. BRADLEY AUST**

University of Minnesota Medical School, Minneapolis

WHEN the diagnosis of cancer is attendant on the appearance of symptoms or signs of the disease, 60 per cent of the patients are doomed to early death within five years after diagnosis. Further, in only 30 per cent of cases of the major forms of cancer is the disease localized when so diagnosed, and in about 50 per cent the lesions are incurable.

The goal of the Minnesota Cancer Detection Center has been to develop a workable, accurate method of examination which includes all internal organs as well as readily accessible external organs. Until a simple serodiagnostic or biologic test is available, such an effort is the only means of detecting malignant disease in its early stages.

Cancer detection implies the finding of malignancies before symptoms or signs herald their presence, as well as diagnosing precancerous conditions. Through the application of a well-conceived routine plan of examination in doctors' offices, we believe several types of serious malignancy can be identified before the usual signs and symptoms appear. More important, the 28 per cent of our population over the age of 45 years who have precancerous conditions can be alerted for close observation or therapy.

During six and one-half years, from March 1, 1948 to September 1, 1954, 6,754 men and women were examined at the Minnesota Cancer Detection Center, and 147 cancers were discovered and their presence proved with biopsy or surgery (table 1). Treatment has been under the direction of the patients' personal physicians. In addition, 2,797 precancerous lesions were detected in 1,894 examinees, an incidence of 28 per cent for persons over 45 years of age.

The age limit of 45 years was established to facilitate the study and assure maximum case finding. Recently the lower age limit for

*Assistant Professor of Surgery and Director of the Cancer Detection Center, University of Minnesota Medical School, Minneapolis, Minnesota.

**Cancer trainee, National Cancer Institute; Department of Surgery, University of Minnesota Medical School, Minneapolis, Minnesota.

Sponsored by the Council of the State Medical Society and supported by a grant from the Minnesota Division of the American Cancer Society.

Presented before the thirty-ninth annual Assembly of the Interstate Postgraduate Medical Association at Minneapolis.

men was raised to 50 years. The high incidence of carcinoma of the cervix in women in the fifth decade of life indicated the advisability of maintaining the lower age limit for women at 45 years.

We have not been able to fulfill the original concept of obtaining a group of completely asymptomatic examinees for observation, since it is obvious that all persons have *some* symptoms during any given period of time. Therefore, the examinees with malignant disease were separated into symptomatic and asymptomatic cases. Of the 147 patients found to have cancer, 79 had symptoms referable to the organ or organ system in which the malignancy was detected and 68 did not. Survival figures are significantly better for the asymptomatic group. Table 2 demonstrates the value of the recheck examination in detecting asymptomatic cancers. Table 3 lists the sites of the cancers found in 147 cases.

Method of Examination

Principles of completeness and economy were important considerations in developing the pattern of examination. Laboratory procedures were reduced to bare essentials, requiring a minimal amount of technical assistance.

TABLE 1

INCIDENCE OF CANCER FOUND AT CANCER DETECTION CENTER, UNIVERSITY OF MINNESOTA MARCH 1, 1948 TO SEPTEMBER 1, 1954

Total patients examined (Men, 3,311; women, 3,443)	6,754	
Total recheck examinations (Men, 4,923; women, 4,740)	9,663	
Total examinations	16,417	
Incidence of cancer	147*	
Over-all incidence of cancer	190	(2.81 per cent)

*Cases found during examination at the Cancer Detection Center; 23.2 per 1000 patients examined (2.32 per cent), or 8.97 per 1000 examinations performed.

CLAUDE R. HITCHCOCK

J. BRADLEY AUST

A detailed history form is completed by the patient prior to his visit to the Center. The patient brings a urine specimen and a stool specimen (collected after three days on a meat-free diet). A routine urinalysis is performed—urine sugar, albumin, microscopic cell study if the urine contains albumin. We tried a benzidine urine test but found that it is not as accurate as microscopic cell study to detect occult urinary bleeding. The stool specimen is examined for occult blood with the guaiac and benzidine tests. Routine blood study includes hemoglobin determination, white cell count, differential count and cell morphology.

Gastric analysis is done in every case. A dose of 0.5 mg. of histamine is given as a stimulant, and a Levin tube is introduced. The standard sodium hydroxide and Töpfer's reagent determination for free hydrochloric acid has proved most satisfactory. The quininium ion urinary excretion test proved too time-consuming.

Chest roentgenograms are made of every patient. Suspicious lesions or single nodules are investigated further with planigrams of the involved area. Sputum is studied by the

TABLE 2

VALUE OF REPEATED RECHECK EXAMINATIONS IN DETECTING CANCER

	ASYMPTOMATIC	SYMPTOMATIC	TOTALS	
			Number	*Per Cent*
Number of cases detected at first examination	32	48	80	54.5
Number of cases detected at recheck examination	36	31	67	45.5

Papanicolaou method. If no diagnosis is forthcoming, bronchograms, bronchial washings, and bronchial biopsy (if possible) are recommended.

All patients who come to the Center are prepared with enemas for proctosigmoidoscopic examination. The sigmoidoscope is inserted to the 25 cm. level, unless peculiar conformity of the bowel (acute angulation) or stricture prevents passage of the instrument. Conditions checked for include (1) small adenomas (2 to 3 mm.); (2) sessile or pedunculate polyps; (3) mucosa which bleeds easily or which is inflamed or ulcerated; (4) diverticula, diverticulitis; (5) hemorrhoids, fissures, fistulas; (6) frank ulcerating carcinomas or intramural tumors. Excision biopsy and fulguration are recommended for all small adenomas and polyps. During the digital examination of the rectum, the prostate is palpated for hypertrophy or nodules.

All women receive a pelvic examination, including bimanual palpation of adnexal areas and direct visual inspection of the vaginal vault and cervix. Any adnexal mass is considered suspicious in this age group, and pelvic laparotomy advised. Suspicious cervical findings include (1) rough area on cervical lip, (2) polyps, (3) blood at the os (not menstruating), (4) atrophic cervical mucosa, (5) erosion of the cervix, and (6) cervicitis.

Papanicolaou smears are made of vaginal secretions and cervical scrapings, and suspicious areas are biopsied. Positive findings on smear examination must be confirmed later by positive biopsy. Suspicious (class 3) smears from an otherwise normal vagina indicate the need for repeated cytologic study every six weeks until results of smear examination are negative or biopsy proves the presence of carcinoma.

On completion of the laboratory work and the proctosigmoidoscopic and pelvic examinations, a clinician examines the patient thoroughly for the remaining problems of a more general nature.

Special Roentgenographic Study

A clinician summarizes the results of examination and determines whether or not further roentgenographic study is needed.

A gastrointestinal series is ordered in cases with the following findings:

1. Histamine achlorhydria and hypochlorhydria (less than 30° free acid).
2. Occult blood in the stool.
3. Family history of gastric carcinoma.
4. Unexplained hemoglobin level of less than 11 gm.
5. Vague gastric symptoms which in any way could be interpreted by the examining physician as being due to gastric carcinoma.
6. Any evidence of undue weight loss.

The air contrast technic is helpful in cases of suspected gastric polyps or small mucosal defects.

Roentgenograms of the colon (barium enema) are indicated in the presence of the following:

1. Abnormal findings on proctoscopic examination.
2. Occult blood in the stool.
3. Unexplained hemoglobin level of less than 11 gm.
4. Family history of malignancy of the large bowel.
5. Vague symptoms which could be interpreted by the examining physician as being due to malignancy of the large bowel.
6. Undue weight loss (10 lb. or more).

In addition to routine barium enema x-rays, all patients found to have polyps are studied by means of air contrast barium enemas.

Intravenous pyelograms are ordered for patients with:

1. Blood in the urine.
2. Costovertebral pain or tenderness.
3. Palpable mass in kidney region.

Results of Six and One-Half Years' Operation

Esophagus and stomach—A total of 14 gastric carcinomas were found, seven in men and seven in women. Achlorhydria or severe hypochlorhydria was present in each case, and a gastrointestinal series was indicated on this basis alone, exclusive of other indications. In only two cases (symptomatic) was the hemoglobin level below 11 gm. Only three asymptomatic patients had occult blood in the

stool, and one patient with symptoms had this finding. Nine patients with gastric cancer were asymptomatic, and five were symptomatic (table 3).

Polypoid carcinomas were found in five of the nine cases in which the patients were asymptomatic, and scirrhous carcinoma in three. Of the five patients with gastric cancer who had symptoms, four had scirrhous carcinoma and one a polypoid lesion. Table 4 presents the results of early diagnosis (asymptomatic patients) compared with those of late diagnosis (symptomatic patients) in the group with gastric cancer. Six of the asymptomatic patients are living and well up to five and one-half years after diagnosis. There is only one survivor in the group with symptoms at the time of diagnosis.

Subtotal gastrectomy offers a good chance for cure of early polypoid lesions. Since virtually 100 per cent of polyp-bearing stomachs are achlorhydric, gastric analysis seems to be a satisfactory method for indicating those cases in which there is a likelihood of polyps. About 50 per cent of polyps larger than 2 cm. in diameter are malignant when found; those 1 cm. or less in diameter when detected are malignant in about 11 per cent.

TABLE 3

SITES OF CANCERS FOUND AT CANCER DETECTION CENTER

SITE	ASYMPTOMATIC	SYMPTOMATIC	TOTAL
Stomach	9	5	14
Colon	13	5	18
Rectum	5	3	8
Small bowel	1	0	1
Lung	3 (metastatic)	1	4
Urinary bladder	1	1	2
Kidney	0	0	0
Breast	8	2	10
Ovary	4	1	5
Cervix	6	2	8
Uterus	0	5	5
Prostate	5	7	12
Skin	6	36	42
Lower lip	0	3	3
Floor of mouth	1	0	1
Thyroid	1	2	3
Hodgkin's disease	1	0	1
Myeloma	1	0	1
Lymphosarcoma	Thyroid, 1 Mesocolon, 1 Stomach, 1	0	3
Lymphatic leukemia	0	6	6
	68	79	147

TABLE 4

SUMMARY OF 14 CASES OF GASTRIC CANCER DETECTED (9 ASYMPTOMATIC, 5 SYMPTOMATIC)

	CASES	
	Asymptomatic	*Symptomatic*
Achlorhydria*	9	5
Hypochlorhydria	1	0
Occult blood in stool	3	1
Roentgenologic diagnosis, first visit	1	2
Roentgenologic diagnosis, subsequent visit	8	3
Scirrhous lesion	3	3
Carcinoid lesion	1	0
Polypoid lesion	5	1
Ulcerating lesion	0	1
Local extension of cancer	1	5
Positive lymph nodes	3	4
Patient alive	6	1
Patient dead	3	4

*Four patients with achlorhydria failed to return for recheck examinations. Gastric cancer developed in all these cases; one patient is living one year later.

Achlorhydria is the most significant criterion indicating the need for roentgenographic study of the gastrointestinal tract in cases of early asymptomatic gastric cancer. This finding is present in 25 per cent of the patients seen at the Center. We do not know of a single case of stomach cancer appearing during the six and one-half years in examinees with normal gastric acidity.

One man seen during the first six months of operation of the Center had total obstruction of the esophagus due to known esophageal carcinoma. He was too ill to undergo examination, and his case is not included in the group of cancers discovered. This was the

only case of esophageal cancer seen during the first five years.

Colon and rectum—Cancer of the rectum and colon was detected in 26 people; 14 patients were men and 12 women. Nineteen lesions (75 per cent) were situated within reach of the sigmoidoscope, 15 at the 9 cm. to 16 cm. level. Four lesions were in the ascending colon or cecum and one was in the descending colon.

Of the 26 patients, 18 had no symptoms of gastrointestinal disease and eight had symptoms referable to this system. Only three of the 18 asymptomatic patients had occult blood in the stool; three of the eight symptomatic patients had this finding. To detect *early lesions not causing symptoms*, examination of the stool for occult blood is not a satisfactory screening device for indicating roentgenographic study.

Routine sigmoidoscopic examination of the rectum and sigmoid has proved to be the most useful screening device for lesions of the large bowel. Table 5 summarizes the examinees in whom cancer of the colon and rectum was detected. Of the 18 symptom-free patients, 17 are living and well up to five years. Only three of the eight with symptoms referable to the colon at the time of diagnosis are living and well (five, five and three years).

There is no etiologic relationship between diverticulitis and carcinoma of the colon. However, inflammatory strictures due to diverticulitis often cannot be distinguished from constricting adenocarcinoma by roentgenographic study. Exploratory laparotomy and resection of the involved area should be performed in cases of potentially obstructing inflammatory lesions, thereby circumventing the risk of unsuccessful differentiation of the benign from the malignant process.

Cervix—Cancer of the cervix was found and proved in eight cases. Six of the women had no symptoms and two had symptoms of pelvic disease when examined (table 6). In two cases in the asymptomatic group, results of study of Papanicolaou smears were negative but suspicious areas noted during cervical inspection indicated the need for biopsy. In only one case (asymptomatic) was the cervix

TABLE 5

SUMMARY OF 26 CASES OF CANCER OF THE RECTUM AND COLON DETECTED

(18 ASYMPTOMATIC, 8 SYMPTOMATIC)

	CASES	
	Asymptomatic	*Symptomatic*
Diagnosed first visit	10	7
Occult blood found in stool	3	3
Hemoglobin level below 12.5 gm.	2	2
Results of proctologic examination positive	14	5
Results of roentgenologic study (barium enema) positive	4*	2**
Ulcerating lesion	5	6
Polypoid lesion	13	2
Lymph nodes positive	4	3
Patient living	17	3
Five years	7	2
Four years	2	
Three years	2	1
Two years	3	
Less than two years	3	
Patient dead	1 (C.V.A.)	5

*Results of roentgenologic study (barium enema) were positive also in 8 of the 14 cases in which proctologic examination disclosed some abnormality.

**Results of roentgenologic study (barium enema) were positive also in 4 of the 5 cases in which proctologic examination disclosed some abnormality.

entirely normal in appearance, the positive Papanicolaou smear constituting the specific indication for biopsy which proved the presence of carcinoma.

Papanicolaou smears were positive in 126 cases of female examinees, and cervical cancer was found and proved in eight of this group (6.6 per cent). It is possible that an indeterminate number of the patients for whom the smears were reported as suspicious will eventually prove to have cervical carcinoma. However, it must be emphasized that visual inspection of the cervix with biopsy of any suspicious area provides an excellent chance of detecting lesions early, particularly when such examinations are repeated annually or semiannually.

Endometrium—Endometrial carcinoma was found in five cases, and all patients had the symptoms and signs of disease (abnormal

TABLE 6

SUMMARY OF 8 CASES OF CANCER OF THE CERVIX AND 5 CASES OF CANCER OF THE ENDOMETRIUM DETECTED (6 ASYMPTOMATIC, 7 SYMPTOMATIC)*

	CASES	
	Asymptomatic	*Symptomatic*
Cancer of the cervix		
Suspicious findings on pelvic examination	5	2
Positive results of study of Papanicolaou smears	4	2
Abnormal findings on pelvic examination and negative results of study of Papanicolaou smears	2	0
Negative results of pelvic examination and positive results of study of Papanicolaou smears	1	0
Squamous cell carcinoma	6	2
Patient living and well	5	2
Five years	2	
Three and one-half years		1
Three years	1	
Two years	2	1
Cancer of the endometrium		
Vaginal bleeding		5
Negative results of study of Papanicolaou smears		5
Positive vaginal findings, exclusive of blood at os		2
Surgical therapy		5
Patient living and well		5
Two years		2
Six months		3

*Positive results of study of Papanicolaou smears were reported in 126 cases (class 3, 113; class 4, 13). Cancer of the cervix or endometrium was proved in 13 cases.

spotting) (table 6). The Papanicolaou smears were negative. Diagnosis was established by dilatation and curettage. All patients are living and well after surgery. A good screening technic is not yet available to detect early endometrial carcinoma. Uterine enlargement and bleeding and discharge from the cervical os remain the only well-established danger signs.

Ovary—Of 100 women who reported back to their physicians with a diagnosis of suspicious adnexal masses, five proved to have carcinoma of the ovary. Four were asymptomatic and one had symptoms (table 7). All cases were detected by means of bimanual palpation, and the surgical specimen disclosed early cystoadenocarcinoma without spread to other tissues. Four patients are living and well. Pelvic examination is the only method for detecting these early ovarian tumors. Laparotomy is necessary to establish the nature of a palpable mass.

Prostate—Suspicious prostatic nodules were noted in 76 cases (table 8). Resection or biopsy of the lesion was done in 25, and carcinoma was proved histologically in 12 cases.

TABLE 7

SUMMARY OF 5 CASES OF CANCER OF THE OVARY DETECTED*

	CASES	
	Asymptomatic	*Symptomatic*
Mass found on pelvic examination	4	1
Multilocular cystadenocarcinoma	2	
Papillary serous cystadenocarcinoma	2	1
Surgical excision	4	1
Patient living and well	3	1
Four and one-half years	1	
Three and one-half years	1	
Three years		1
Two years	1	
Patient dead	1	0

*Suspicious adnexal masses were reported in 100 cases. Of these 100 patients, 45 underwent surgery; 5 cases of cancer were proved.

We accept only histologic proof of malignancy, not merely clinical impression. Nine patients have been treated for prostatic carcinoma on the basis of clinical evidence alone.

Five of the 12 patients with proved prostatic cancer were asymptomatic, and seven had symptoms of prostatic obstruction. Two of the symptom-free patients had bony metastases, as did two of the patients with symptoms. One of the seven symptomatic patients is dead, as are two of the five asymptomatic patients. A satisfactory screening test for prostatic cancer is not available. Unfortunately, in many cases widespread bony metastases are present at the time symptoms of prostatic obstruction appear. It is only conjectural to assume that repeated examination will alter the outcome of prostatic cancer significantly.

Skin—Skin cancer was diagnosed at the Center in 42 cases (table 9). The lesions were basal cell carcinomas in 31, and squamous cell carcinomas in 10. One pigmented nevus proved to be a malignant melanoma. All these skin lesions were small and localized. Treatment has been successful, and all the patients are living and well at present. Thirty-six of the 42 patients were aware of the lesion, but most considered it benign and of no consequence.

Senile keratosis of the skin is considered a precancerous lesion, and it was noted in 401 examinations. A total of 325 pigmented nevi exposed to chronic irritation were reported, but only one case of malignant melanoma has been demonstrated.

Diagnosis of skin cancer presents no problem when clinicians submit biopsy specimens of all suspicious lesions for histologic study.

Lung—In the first six years of function of the Center, only one primary carcinoma of the lung was found. The lesion was far advanced, and the patient had obvious symptoms of pulmonary malignancy. Three metastatic carcinomas were detected, one a metastatic melanoma (not the case previously mentioned) and the other two metastatic hypernephromas. Not a single case of asymptomatic primary carcinoma of the lung has been detected, but one examinee was misdiagnosed. This is unusual, and perhaps is due to the exceptionally good detection of lung lesions by the mobile unit chest survey which is extensively used in Minnesota. Willingness on the part of the examinees at the Center to participate in a cancer detection program indicates a likelihood that they also availed themselves of the chest x-ray examination.

There are no pathognomonic symptoms of *early* lung cancer. Symptoms present during the earliest phases of lung cancer are identical to those of common respiratory diseases. They often respond to nonspecific treatment, and serious delays in accurate diagnosis and treatment are thereby fostered. The highly lethal nature of cancer of the lung makes it imperative that clinicians exercise a high degree of suspicion toward silent lung nodules (coin

TABLE 8

SUMMARY OF 12 CASES OF PROSTATIC CANCER DETECTED

	CASES
Suspicious prostatic nodules noted	76
Carcinoma proved histologically	12
Lesion treated as cancer but not proved histologically	9
Patient under observation by family physician	32
Lesion proved benign	12
Patient asymptomatic at time of examination	5
Patient symptomatic at time of examination	7
Patient living and well	9
Asymptomatic group	3
Symptomatic group	6

TABLE 9

SUMMARY OF 42 CASES OF SKIN CANCER DETECTED

	CASES
Total suspicious skin lesions	558
Cancers proved and treated	42
Squamous cell carcinoma	10
Extremities	2
Trunk	1
Head and neck	7
Basal cell carcinoma	31
Extremities	3
Trunk	3
Head and neck	25
Malignant melanoma	1
Patient alive	42

lesions) and other suspicious pulmonary changes if a significant increase in five year survival is to be effected.

Breast—Suspicious breast lesions were found in 173 women. Carcinoma was proved at surgery in 10 cases (5.7 per cent), and 88 lesions were found to be benign (table 10). Diagnosis is not yet definite in 26 cases. Eight of these tumors were unknown to the patients at the time of examination. Eight patients are living and well. One died of cerebral metastases 15 months after surgery. At present, periodic physical examination of the breasts is the only proved method of detecting this form of cancer.

Urinary tract—The kidney is a difficult organ to study with the usual methods of cancer detection. Routine urinalysis to detect urinary tract bleeding has not been adequate as an indication for advanced roentgenologic study. Most lesions of the kidney are large enough to be palpated during physical examination before they have invaded the renal pelvis and caused urinary tract bleeding. The diagnosis was missed in two cases in which adenocarcinoma of the kidney developed subsequently. In the absence of an adequate screening technic, and because the widespread use of pyelography is unfeasible, we probably will not improve the figures for diagnosing cancer of the kidney in an asymptomatic stage. No testicular or penile cancers have been found.

Lymphatic system—Of six patients found to have lymphatic leukemia, four had palpable lymph nodes at the time of examination (table 11). All had symptoms. Five patients had symptoms of a mass, pain or weakness. In 113 cases the lymphocyte count was more than 45 per cent, and 107 patients in this group have not developed lymphoma to the present time. Four of the six patients with leukemia are alive up to six years after time of treatment.

Thyroid—Three cases of papillary adenocarcinoma of the thyroid were proved at surgery, and one lymphosarcoma of the thyroid was found (table 11). In these cases, the thyroid gland was reported as being the site of suspicious nodules. A total of 191 thyroid adenomas were reported. We believe about 7 per cent of palpable, single thyroid nodules will prove to be malignant (University of Minnesota study).

TABLE 10

SUMMARY OF 10 CASES OF BREAST CANCER DETECTED

	CASES
Suspicious breast lesions	173
Surgery	98
Proved carcinomas	10
Asymptomatic group	8
Symptomatic group	2
Patient under observation by family physician	26
Results of subsequent examination negative	27
Patient dead of asymptomatic breast cancer	1
Patient dead of other cause	1
Lesion found by family physician during examination interval	3*
Patient failed to return for recheck; cancer developed	2*
Lesion missed by Cancer Detection Center examiner	2*

*Patients living.

TABLE 11

SUMMARY OF MALIGNANT LYMPHOBLASTOMAS DETECTED

		CASES
Lymphatic leukemia		6
Asymptomatic group	0	
Symptomatic group	6	
Positive physical findings	5	
Elevated white blood cell count	6	
Patient living and well	4	
Six years	1	
Five and one-half years	1	
Three and one-half years	1	
Two years	1	
Lymphosarcoma		3
Asymptomatic group	3	
Symptomatic group	0	
Thyroid (living and well four years)	1	
Mesocolon (living and well six months)	1	
Stomach (living and well one year)	1	
Hodgkin's disease, asymptomatic (Obscure palpable node, living and well one year)		1
Multiple myeloma, asymptomatic (Bence Jones proteinuria; bone marrow diagnostic; patient living and well one year)		1

Precancerous lesions—Table 12 lists eight types of lesions considered to be precancerous and the number of cases in which they were detected. It is impossible to calculate the potential salvage in this large segment of the over-all group (28 per cent) through prevention of malignancy by application of appropriate therapy during the premalignant stage.

TABLE 12

PRECANCEROUS LESIONS DETECTED

	CASES
Adenomas and polyps of rectum and colon	1,501
Gastric polyps	24
Kraurosis vulvae	36
Leukoplakia	318
Pigmented nevi in areas of irritation	325
Polyps of vocal cords	1
Senile keratosis	401
Thyroid adenoma	191
TOTAL	2,797*

*Total patients with precancerous lesions, 1,894 (28 per cent).

Discussion of Results of Six and One-Half Years' Operation

It is to be expected that a few cancers might develop in such a manner that detection center procedure would not screen out the lesions, or that failure of an examinee to cooperate would result in late diagnosis. Also, occasional misinterpretation of roentgenograms might result in undue delay in establishing the histologic nature of a questionable lesion.

Table 13 separates into various categories the over-all number of patients in the Center population known to have cancer (190). There were 147 malignancies detected at examination, or 77.4 per cent of the total cases of cancer. In 46 per cent of the cases detected, the lesions produced no symptoms; the remaining 54 per cent of patients found to have cancer had symptoms referable to the site of malignancy.

The 22.6 per cent of the total number of known cancers not accredited to detection in the examination procedure can be separated into three groups:

1. Patients without signs or symptoms of malignant disease at the time of examination at the Center in whom the lesion became manifest during an interval between examinations and was diagnosed by the patients' personal physicians (13.2 per cent of total).

2. Patients failing to return for recheck examinations even though specific criteria indicated the value of follow-up procedures (5.2 per cent of total).

3. Patients in whom a cancer was frankly missed during examination at the Center and became obvious within two months (4.2 per cent of total).

It is apparent that 17 per cent of the total number of known cancers represent failure of examination methods, and an additional 4.2 per cent were missed because of error by the examining physician.

Of the 147 cancers correctly diagnosed, 39 were established by roentgenograms of one

TABLE 13

OVER-ALL INCIDENCE OF CANCER AMONG 6,754 PERSONS EXAMINED

	NUMBER	PER CENT OF TOTAL CASES OF CANCER
Total number of cases attributed to detection by Cancer Detection Center	147	77.4
Asymptomatic cases detected by Cancer Detection Center	68	46.2
Cases not detected by Cancer Detection Center	43	22.6
Total cases of cancer in which patients were without signs and symptoms during examination but in whom lesions became manifest in interval between rechecks		13.2
Cases not diagnosed through Cancer Detection Center because of failure of patient cooperation		5.2
Cases of cancer frankly missed during examination at Cancer Detection Center		4.2

TABLE 14

CASES IN WHICH PATIENTS FAILED TO RETURN FOR RECHECK OR FOLLOW-UP PROCEDURES AND IN WHICH CANCER DEVELOPED SUBSEQUENTLY

SITE OF LESION	CASES	INTERVAL BETWEEN LAST C.D.C. EXAMINATION AND DIAGNOSIS (MONTHS)	REMARKS
Stomach	4	24; 63; 64; 50	3 achlorhydric; 1 hypochlorhydric; 3 dead
Colon	2	6; 24	1 dead
Breast	2	18; 20	
Pancreas	1	25	Patient dead
Meninges	1	18	

kind or another. Only two of the frankly missed cases were dependent on x-ray methods for diagnosis, and this constitutes 4.9 per cent failure for roentgenologic diagnosis during the six and one-half years of operation of the Center. This figure compares favorably with diagnostic experience in the x-ray department at the University of Minnesota Hospitals. All roentgenologic diagnostic methods have specific limitations, and clinicians responsible for patients must appreciate the necessity of bringing other more specific methods (microscopic tissue examination) to bear in questionable cases.

Of the cancers correctly diagnosed, 103 were found either during physical examination or by means of laboratory study. If we consider 21 of the missed lesions as failures of physical diagnosis or laboratory diagnosis, this represents 15.7 per cent inaccuracy as far as missing malignancy is concerned. It must be remembered, however, that many lesions were reported as suspicious (prostate, ovary, breast, thyroid) and proved to be benign. Again, the shortcomings of gross palpation or inspection are obvious, and the necessity for both histologic and cytologic verification is amplified.

A small group of patients failed to follow recommendations for follow-up procedures or recheck examinations, and carcinoma developed subsequently in 10 of these cases. Gastric cancer developed in four cases in which the patients were either achlorhydric or markedly hypochlorhydric. These lesions appeared as late as 64 months after the patient's last visit to the Center. Three of the patients are dead. Table 14 presents this group of patients in detail.

Another segment of the Center population had examination results which were negative for malignant disease, but during the 12 month interval between first examination and recheck examination frank symptoms of malignancy developed. The lesions were diagnosed and proved by the patients' personal physicians. It is interesting that all cancers of the gallbladder or pancreas were diagnosed under conditions other than the examination at the Center. Unfortunately, there are no criteria whereby we can focus our attention on a specific group with increased tendency to devel-

TABLE 15

CASES IN WHICH MALIGNANCY DEVELOPED BETWEEN FIRST EXAMINATION AND RECHECK EXAMINATION

SITE OF CANCER	NUMBER OF CASES
Kidney	1
Gallbladder	2
Tonsil	1
Thyroid (lymphosarcoma)	1
Prostate	2
Corpus uteri	2
Pancreas	3
Breast	3
Lower lip	1
Urinary bladder	1
Ovary	2
Eye (melanoma)	1
Brain (metastasis from melanoma)	1
Primary site unknown, metastatic carcinoma	1
Carcinoid appendix	1
TOTAL	23

opment of this form of malignancy. Our results bear out the universally grave prognosis in malignancy of the biliary and pancreatic systems. Table 15 lists the lesions which developed under these circumstances, and table 13 shows that this group represents 13.2 per cent of the total number of cancer patients examined at the Center. Table 16 presents the failures of diagnosis at the Center. This small group constitutes 4.2 per cent of the total cancer patients. The lesion of the colon was misdiagnosed as diverticulitis by the roentgenologists, and the lung cancer was missed twice by x-ray diagnosticians at six month intervals. Failure to advise thoracotomy in the case of this suspicious lesion rests with the Center.

Table 17 shows the mortality rates for the various forms of cancer during the six and one-half years. Since all skin lesions found were early and no deaths or serious recurrences occurred, we have not included cancer of the skin in calculating the mortality percentages. This omission leaves only major forms of cancer for purposes of evaluation. There were 17 deaths among the 40 patients with cancer not diagnosed at the Center, a mortality rate of 42.5 per cent. In comparison, in the *symptomatic* group found at the Center, the mortality rate is 30.2 per cent; in the *asymptomatic* group there were only 11 deaths among 62 patients, or a 17.7 per cent mortality rate. Even now the pronounced trend toward lowered mortality is apparent when malignant lesions are diagnosed and treated before symptoms or signs develop.

TABLE 16

FAILURES OF DIAGNOSIS AT CANCER DETECTION CENTER*

SITE OF CANCER	CASES	REMARKS
Colon	1	Diverticulitis
Kidney	1	Lower urinary tract symptoms
Lung	1	Failure of x-ray diagnosis; patient dead
Breast	2	Nodule missed
Skin	3	Failure to recommend biopsy; 1 patient dead of coronary attack

*Lesions subsequently were proved elsewhere within two months of the examinations at the Cancer Detection Center. Cases include those in which appropriate or adequate follow-up procedures were not advised.

Summary

1. During six and one-half years' operation of the Cancer Detection Center at the University of Minnesota, 147 cases of cancer were found in a total of 16,417 examinations performed on 6,754 persons. This represents 23.2 cancers per 1000 patients examined (2.32 per cent), or 8.9 cancers per 1000 examinations performed.

2. Of the persons found to have cancer, 68 were symptom-free with regard to the organ or organ system in which the lesion was found. In 79 cases the patients had symptoms indicating a likelihood of cancer in the organ or organ system involved. In the asymptomatic group 36 cancers were found at recheck examination, indicating the value of repeated

TABLE 17

OVER-ALL MORTALITY RATES

	NUMBER	PER CENT OF TOTAL CASES OF CANCER
Deaths among patients not diagnosed at Cancer Detection Center, minus cases of skin cancer (40 cases)	17	**42.5**
Deaths in symptomatic group, minus skin cancer cases (43 cases)	13	**30.2**
Deaths in asymptomatic group, minus skin cancer cases (62 cases)	11	**17.7**
Deaths in total group of cases detected at Cancer Detection Center (147 cases)	24	16.3
Deaths in total group of cases (190)	41	21.5

examinations to detect early malignancy.

3. Only in cancer detection centers or cancer prevention clinics are large numbers of persons surveyed for cancer while they are without symptoms of disease. It seemed of value to emphasize the difference in survival between symptomatic and asymptomatic examinees found to have cancer in this study.

4. Six of nine asymptomatic patients found to have gastric cancer are alive and well five years after surgery. Only one of five patients with gastric cancer who were symptomatic at the time of diagnosis is alive. Of 18 patients with cancer of the colon who were free of symptoms at the time of diagnosis, 17 are living and well (11 for more than three years), whereas only three of the eight patients found to have cancer of the colon who had symptoms at the time of diagnosis are living. These figures appear to substantiate the increased value of early diagnosis in terms of survival.

5. Of the total group examined, 28 per cent had precancerous lesions. The value of treating these lesions is incalculable.

6. Of 190 cancers detected during the six and one-half years (during examination at the Center or during recheck intervals by the patients' personal physicians), 17.4 per cent are considered failures of the Center. Roentgenologic technics failed in 4.9 per cent of the 39 cases in which diagnosis was established by this modality. Misinterpretation of x-ray changes was the responsible factor. Of the cases detected by means of physical examination and laboratory studies (108), 15.7 per cent must be considered failures for these methods.

7. There were 17 deaths among the 40 patients in whom the malignant disease was not detected in the Center for one of several reasons (42.5 per cent). This mortality rate contrasts with 30.2 per cent among patients with major cancers in the *symptomatic* group detected at the Center. The *asymptomatic* group shows only a 17.7 per cent mortality rate. These calculations were made after eliminating cancer of the skin in each category.

8. We believe that several types of serious malignancy can be identified in advance of their usual signs and symptoms through the application of a well-conceived, routine cancer detection examination performed annually.

REFERENCES

1. Ballin, J. C., Feinstein, R. N. and Warner, Nancy E.: Clinical evaluation of the blood cell carboxypeptidase inhibitor test for malignant neoplasia. Cancer Research 13:7984-788 (November) 1953.
2. Berkson, Joseph and Comfort, Mandred: The incidence of development of cancer in persons with achlorhydria. J. Nat. Cancer Inst. 13:1087 (March) 1953.
3. Chipps, H. D.: The Washington State Tumor Registry and its role in problems regarding gastric cancer and cancer research. J. Nat. Cancer Inst. 10:439-441 (October) 1949.
4. Cooper, W. A.: Abstract of color film: The exfoliative cytologic method in the diagnosis of gastric cancer. J. Nat. Cancer Inst. 13:1047 (March) 1953.
5. Cromer, H. E., Jr., Comfort, M. W. and Butt, H. R.: Gastric acidity in cases of adenomatous gastric polyp. J. Nat. Cancer Inst. 10:497-503 (October) 1949.
6. Gardner, E. J., Woolf, C. M. and Shaffer, J. O.: The inheritance of cancer involving different areas of the human gastrointestinal tract. J. Nat. Cancer Inst. 13:1089-1093 (March) 1953.
7. Guiss, L. W.: Value of mass chest roentgen-ray survey methods in control of lung cancer. Cancer 5:1035-1040 (September) 1952.
8. Hitchcock, C. R. and Aust, J. B.: Cancer detection; a report from the Cancer Detection Center, University of Minnesota. Minnesota Med. 37:243-250 (April) 1954.
9. Hubbard, T. B., Jr. and State, David: Cancer detection; report from the Center at the University of Minnesota. Minnesota Med. 35:925-929 (October) 1952.
10. Robbins, G. F., MacDonald, Mary C. and Pack, G. T.: Delay in the diagnosis and treatment of physicians with cancer. Cancer 6:624-626 (May) 1953.
11. Segal, H. L., Miller, L. L. and Morton, J. J.: Detection of achlorhydria by tubeless gastric analysis. J. Nat. Cancer Inst. 13:1079-1086 (March) 1953.
12. Stillwell, G. G.: Tests for cancer. Minnesota Med. 36:623-624 (June) 1953.
13. Wigh, Russell and Swenson, P. C.: Gastric photofluorography for adenomas and cancer. Its place in a cancer detection program. J. Nat. Cancer Inst. 13:1075-1077 (March) 1953.
14. Hay, L. J.: Polyps and adenomas of the stomach. Surgery 33:446-467 (March) 1953.

Preoperative Preparation of the Pediatric Patient

M. DIGBY LEIGH

Children's Hospital, Los Angeles

As the general practitioner is called on more and more to administer anesthetics, and 20 to 25 per cent of surgical procedures are performed on infants and children, it is timely to discuss some essentials for proper preparation of patients in this age group for surgery.

M. DIGBY LEIGH

Psychotherapy

Pediatric wards of hospitals are usually very attractive, with gay murals on the walls. Doctors, nurses, therapists and other personnel approach the child with a kindly and understanding attitude. This pleasant environment helps the child to withstand with equanimity the unusual and sometimes unpleasant experiences of hospitalization. The child is told preoperatively what his condition will be when he awakens; for example, if his eyes are to be bandaged, this is explained to him and repeated as he is regaining consciousness. Explanations such as this give him a feeling of security and a reposed recovery period.

Gastrointestinal System

Food—Solid food by mouth, including milk, should not be given to infants for four hours before operation; for children more than two years of age this period should be six hours. Clear fluids such as glucose in water, and apple juice, may be administered up to two hours preoperatively.

When the exigencies of surgery demand immediate operation in spite of food or fluid intake, it is advisable to place the patient in the Trendelenburg position on his side and commence anesthesia. Immediately after the in-

duction of anesthesia, the back of the throat is stimulated with a metal aspirator to induce retching and vomiting.

Some anesthesiologists prefer to wash out the stomach before any anesthesia is administered. Others anesthetize the child to a deep stage of anesthesia and insert an endotracheal tube to guard the airway, should emesis occur later during the operation.

Here is an interesting account received:

I am ashamed of myself, really. The boy had breakfast at 8, broke his wrist at 8:30, and we were reducing it at 4. I was aware that he more than likely had a full stomach; however, for the 10 minutes I thought it would take to reduce the fracture, I dismissed a tube as too fancy. I used a little PENTOTHAL® induction and enough anectine to keep him apneic, then nitrous oxide and oxygen—quite enough anectine, as a matter of fact. They took nearly an hour (for a simple Colles'!) but it doesn't excuse me, nevertheless. Near the finish he got a little obstructed. I inserted an airway and there was some improvement. Then I noted a decreased expansion of the right upper chest. My fear, silent vomiting, was confirmed by looking in the pharynx with a scope. There were just a few flecks. I could see clear down the trachea and it looked clear, but I intubated him anyway. After suctioning mucus I got some easily recognized yellow vomitus (corn flakes, I guess). Then the stomach emptied, filling the kidney basin, my shoes, etc. We sucked, he coughed, I rinsed a little saline into the bronchi. Finally breath sounds were clear. We took a chest x-ray with a portable machine, and it was later reported as showing some hazing in the right upper lung. This cleared with bed rest and antibiotics. Moral: Never again—always a tube if I suspect something is in the stomach!

Stomach distention—When there is distention of the stomach brought on by respiratory obstruction when the child swallows considerable air, or by intestinal obstruction, a stomach tube should be passed. Generally, this is done soon after induction of anesthesia. If intestinal obstruction is present, the gastric contents may be regurgitated silently during anesthesia and trickle down into the lungs.

Enema—An enema should be given the night before operation if the patient did not have a bowel movement that day. The lower bowel is very active in infants and young children, and a soapsuds enema ordinarily suffices. If rectal surgery is planned, two or three soapsuds enemas (or at least until the fluid returns clear) are given on the morning of operation.

Respiration

Premature infants, who often have inadequately expanded lungs, and children with bronchiectasis require prophylactic dosages of antibiotics before operation. Bronchiectatic patients should have postural drainage the day before operation and also the following morning. In fact, bronchoscopic aspiration may be necessary just prior to operation if secretion is copious.

Circulation

Heart disease—Like other children, those with congenital cardiac anomalies or with myocardial damage from either rheumatic fever or scarlet fever may require a surgical procedure. For obvious reasons, most such patients are brought to pediatric hospitals.

Preoperatively, antibiotics are administered and adequate bed rest is provided. If paroxysmal supraventricular tachycardia is present, CEDILANID® is given in a dosage of 0.01 mg. per pound of body weight.

In congenital cardiac disease with cyanosis, oxygen is administered by mask and bag before the anesthetic agent is given.

Transfusions—Blood transfusions are required by anemic patients and when the operative procedure will entail considerable loss of blood. Preparation for this requires matching of the blood beforehand. If Rh positive blood is given to an Rh negative infant, antibodies to the Rh factor may develop.

When large amounts of blood are transfused, one should be prepared to counteract with calcium gluconate the tetany due to blood calcium reduction by the citrates. A very forcible warning is interjected here: *Do not confuse calcium gluconate with calcium chloride.* Calcium chloride is a very strong cardiac

stimulant and its use is quite hazardous.

If blood loss is anticipated, the most reliable method for blood transfusion in the case of an infant is to cut down on the saphenous vein just anterior to the medial malleolus of the ankle and insert either a cannula or a polyethylene tubing. This cut-down may be done while the infant or child is conscious by injecting a local anesthetic intradermally and subcutaneously. Many small patients have died because an intravenous needle was not inserted before operation. Rarely, cannulae may have to be inserted in two veins, for blood loss during operation may be very rapid and one portal of entry inadequate.

During the first few days of life, the bleeding time tends to be increased slightly, and the coagulation time increased noticeably. This is especially true if the mother was not given vitamin K. If an operation is necessary on such newborn infants, 1 mg. of vitamin K is administered intramuscularly or intravenously daily to promote thrombin production by the liver and to reduce operative bleeding somewhat.

Always keep in mind that infants withstand blood loss poorly. First, they have a low blood volume (approximately 500 cc. at birth), so a comparatively small blood loss is a significant percentage; second, they are naturally hypotensive.

Fluid and electrolyte balance—In estimating fluid balance, consider recent weight loss and the general appearance of the patient. Does he look ill? Has he sunken, roving eyeballs? Has he depressed fontanels? Has his skin lost its elasticity (easily tested by lifting the skin to see if it remains pinched up)? These conditions usually indicate water deficiency. Proper electrolyte and fluid balance can be maintained in a practical manner by administering an isotonic solution consisting of two-thirds 5 per cent glucose in water and one-third normal saline solution. This precaution to reduce the quantity of sodium ion is important in infants, since the immature kidneys cannot handle readily the excretion of the sodium. Sodium retention causes water retention, and water-logging has been the cause of many deaths.

In the newborn, saline infusions are either omitted or used sparingly.

If vomiting is protracted, such as in a case of pyloric stenosis, a more exact picture of the electrolyte balance must be obtained, because there can be both a large loss of chlorides and a lesser loss of sodium and potassium, with a resultant compensatory increase in alkali reserve to make up for chloride loss.

Therefore, measuring the carbon dioxide-combining power and chlorides, together with serum sodium and potassium, gives a picture of the electrolyte balance. Before surgery, fluid and electrolyte balance should be restored. Normal saline solution, about 60 cc. per pound of body weight, is given by intravenous drip over a 24 hour period, together with a blood transfusion, approximately 10 cc. of blood per pound of body weight, to correct anemia and hypoproteinemia.

After restoring fluid and electrolyte balance, AMIGEN® solution can be administered parenterally for protein replacement, and intravenous potassium chloride for correction of potassium deficiency. Details of this more hazardous treatment must be left to a more exacting explanation of electrolyte balance. Such careful preoperative treatment increases considerably the number of successful results from surgery.

Urogenital System

At times albumin is found in the catheterized urine. One should determine whether the origin is hypostatic or organic. Numerous infants show urinary ketone bodies, even on the omission of one feeding, and may require 5 per cent glucose in water, although the complete elimination of these bodies cannot always be expected.

Often, children two years of age and older are brought to the operating room with an overdistended bladder. These children can retain urine in the bladder until it reaches to the umbilicus. The lower part of the abdomen is distended, firm, and dull to percussion. All children who show this bladder tumor should be catheterized preoperatively. Infants, on the other hand, infrequently exhibit an overdistended bladder.

Hormones

Adrenocortical—In recent years some older children have had long courses of cortisone or ACTH therapy for diseases such as rheumatoid arthritis. It is important to determine whether such treatments were given within the previous few months. If so, these children should be given cortisone or hydrocortisone two or three days preoperatively and postoperatively, in dosages similar to those they previously received. Otherwise, a sudden collapse on the operating room table may occur.

Diabetes—If possible, the urine should be examined for sugar and diacetic acid, and the blood for sugar, carbon dioxide-combining power, and chlorides. The diabetes should be brought under control with insulin and antiacidotic fluids, such as sixth molar sodium lactate. Correct any anemia with blood transfusions and treat any infections with antibiotics. On the morning of operation, give enough insulin to metabolize the glucose to be given. Usually, this amount has been worked out for each patient (1 unit of insulin metabolizes about 2 gm. of glucose). Sweetened orange juice is divided into three portions and the first portion is given 15 minutes after the insulin, the second portion 45 minutes later, and the last portion after another 45 minutes. The operation usually is done one and one-half hours after this last third of the orange juice is given.

Metabolism

Children seldom have hyperthyroidism, but if they do, a course of treatment with propylthiouracil is advisable, just as in the adult.

Some children have a raised basal metabolic rate due to high temperature. Every degree of rise in temperature above normal raises the rate of metabolism 7 per cent. It is advisable to lower the temperature of these hyperpyrexia patients by removing coverings, and at times cooling them off with a fan. Otherwise, rapid, exhausting breathing and even convulsions may occur during anesthesia.

TABLE 1

PREOPERATIVE MEDICATION FOR INFANTS AND CHILDREN

AGE	WEIGHT (LB.)	DRUG			
		NEMBUTAL® or Seconal (rectal capsule or suppository)	Morphine (Hypodermically)	Demerol (Intramuscularly)	Scopolamine or atropine (intramuscularly or subcutaneously)
Newborn	3-7				1/600 gr. (0.1 mg.)
1-4 mo.	10-14	¼ gr. (15 mg.)			1/600 gr. (0.1 mg.)
4-12 mo.	14-21	¼ gr. (15 mg.)			1/600 gr. (0.1 mg.)
1-2 yr.	30	½ gr. (30 mg.)	1/60 gr. (1 mg.)	10 mg.	1/450 gr. (0.15 mg.)
2-3 yr.	34	¾ gr. (45 mg.)	1/60 gr. (1 mg.)	15 mg.	1/450 gr. (0.15 mg.)
3-4 yr.	38	¾ gr. (45 mg.)	1/40 gr. (1.5 mg.)	20 mg.	1/300 gr. (0.2 mg.)
4-5 yr.	44	1 gr. (60 mg.)	1/30 gr. (2 mg.)	25 mg.	1/300 gr. (0.2 mg.)
5-6 yr.	50	1 gr. (60 mg.)	1/20 gr. (3 mg.)	30 mg.	1/300 gr. (0.2 mg.)
6-8 yr.	55	1 gr. (60 mg.)	1/15 gr. (4 mg.)	35 mg.	1/200 gr. (0.3 mg.)
8-9 yr.	60	1¼ gr. (75 mg.)	1/12 gr. (5 mg.)	40 mg.	1/200 gr. (0.3 mg.)
9-10 yr.	65	1¼ gr. (75 mg.)	1/10 gr. (6 mg.)	45 mg.	1/200 gr. (0.3 mg.)
10-11 yr.	74	1½ gr. (90 mg.)	1/10 gr. (6 mg.)	50 mg.	1/200 gr. (0.3 mg.)
11-12 yr.	80	1½ gr. (90 mg.)	1/10 gr. (6 mg.)	50 mg.	1/150 gr. (0.4 mg.)

Use a combination of a barbiturate, an opiate or opiatelike, and a belladonna drug.

If the child is underweight or marantic, reduce the dosage.

Preoperative Medication

Patients who have had proper psychotherapy, as they usually do under the care of a general practitioner who has known them for years, will receive excellent results from preoperative medication. When studying the preoperative medication outlined herein, keep in mind that the table is offered only as a guide, and that smaller dosages should be used until experience is gained.

In early experiences with morphine, hospital staffs have endeavored to withdraw 1 or 2 minims of the dissolved concentrated drug. This was both inaccurate and dangerous. It is suggested that this drug be diluted and the required portion injected.

For your guidance, the following methods of premedication are offered:

Barbiturates (rectally).

1. Pentothal or SURITAL®, rectally: 2½ per cent of 5 per cent solution, giving 10 to 20 mg. per pound of body weight. This method is desirable for very disturbed patients. A useful practical point, when it is desired to retain rectal fluids, is to strap the buttocks together firmly with two pieces of adhesive tape 1¼ inches wide.
2. SECONAL®, rectally: (a) solution, 2 to 4 mg. per pound of body weight in a 5 per cent solution; (b) capsule, which should be perforated with a pin and inserted well into the rectum; otherwise the capsule may be found later in the infant's diaper.

Combination of a barbiturate, an opiate or opiatelike drug, and a belladonna drug (see table 1).

As already stated, the dosages of these drugs must be modified to suit the individual patient. For example, in the case of a cachectic child the dosage may have to be reduced. In fact, sometimes any respiratory depressant drug such as Seconal, DEMEROL® or morphine may have to be omitted.

It is hoped that the foregoing suggestions will be of assistance, and will provide a basis for insuring greater safety for the pediatric patient during surgery.

BEWARE!

Fraudulent Magazine Solicitations

A magazine solicitor calling himself Fred Carter has been soliciting new and renewal subscriptions for general magazines and certain medical journals including POSTGRADUATE MEDICINE.

This fraudulent solicitor has been collecting cash with orders and giving printed receipts in the name of Medical Service, Inc., 1000 Park Avenue, New York 18, New York (not to be confused with Medical Publishers Service, 18 W. 55th St., New York 19, upon whose good name this fraudulent solicitor is attempting to operate).

The money he has collected has not been turned in, nor have the subscribers been reported to the publishers involved.

The National Better Business Bureau conducted an investigation and found that there was no such company listed in New York City directories and all mail sent to the above address has been returned by the post office.

Should any of our subscribers be solicited by this individual, immediately get in touch with your local Better Business Bureau or the police.

Lead Poisoning in Young Children

HEYWORTH N. SANFORD*

University of Illinois College of Medicine, Chicago

HEYWORTH N. SANFORD

LEAD poisoning is not uncommon in children, and there is a general impression that its incidence is increasing. Certainly, in many localities, while the increase in the incidence may be due to an increased awareness of the condition, the disease seems to be observed more frequently. It is a serious condition, and can result in death or permanent neurologic disability. It is entirely preventable, and could be eliminated if the public were made fully aware of its danger.

Lead may enter the body through the gastrointestinal tract, the skin or the lungs. It rarely enters through the skin, and this source of the disease may be ignored. When the disease occurs through the lungs it is usually due to inhalation of the salts contained in the fumes and smoke emitted by the burning of storage battery casing for fuel. The usual manner in which lead enters the body is through the gastrointestinal tract. When it enters in this way, lead salts are formed which are largely absorbed. However, this absorption is usually slow and may not produce any clinical manifestations for some time. The onset of the symptoms of lead poisoning depends more on the length of time the lead stays in the gastrointestinal tract than on the amount ingested. A single quantity of lead ingested at one time may not produce any symptoms, while the same amount ingested over a longer period may produce definite symptoms.

In cases in which lead poisoning occurs through the gastrointestinal tract of children, the chief source of the lead is paint on window sills, recently repainted walls, or ceilings from which paint has chipped off and fallen into

*Department of Pediatrics, University of Illinois College of Medicine, Chicago, Illinois.

the children's reach. Outside house paint, particularly white, may contain considerable amounts of lead. This would be a potent source of poison except that only under certain circumstances, such as perhaps drinking fresh house paint, would the child have much access to it. At present, most interior wall paint usually is free of lead, but this metal can still be found in some of the less modern paints in older houses, particularly those containing chrome green or chrome yellow. Home owners themselves might also repaint their walls with paint containing lead. Other less common sources are lead pipes, repainted toys, and furniture on which lead paint has been used, or various coloring materials containing lead.

Another interesting feature of lead poisoning in children is that the symptoms frequently are most apparent in the summer months, that is, between June and September. This is caused by the lead in the body being absorbed, transported, deposited and excreted in much the same manner as calcium. Conditions that favor calcium retention simultaneously favor deposition of lead in the bones, and, conversely, factors which tend to produce mobilization of calcium from the bones also tend to liberate lead from its skeletal deposits. Infections or metabolic disorders which cause acidosis will liberate lead and calcium from the sites of deposit. This release of lead into the tissues will cause an acute exacerbation of symptoms and may occur after or during acute infections. In summer, fever and heat may cause vasodilatation and hasten liberation of lead from the bones, or the antirachitic effect of solar radiation, which is greatest in this period, may result in increased absorption of lead from the intestine.

Except in instances of acute lead poisoning, which is uncommon in children, the usual symptoms are similar to those which occur in any chronic disease. They develop insidiously and intermittently. The slow absorption and gradual accumulation of lead in the blood and soft tissues produce the clinical features. Lead that is absorbed from the bowel enters the portal circulation and is mostly excreted by the liver. Lead that reaches the systemic circulation is deposited in the bones and in soft tissues, such as the liver, kidney, pancreas and brain. In the brain, there is usually an intense edema, punctate hemorrhages, gliosis and areas of focal necrosis. In the peripheral nerves, the axon and the whole cell may be destroyed.

The lead is slowly transferred from the soft tissues to the bones where it is deposited as insoluble tertiary lead phosphate. Decalcification is also associated with a release of lead from the bone. This is a reversible process—the symptoms of lead poisoning depending on the amount of lead in the soft tissues and on its transportation from soft tissues to bone or from bone back to soft tissues. This accidental or incidental mobilization of lead from the tissues may produce irreversible and often fatal sequelae.

Lead also has a specific action on the blood. It is combined or absorbed onto the membrane of the red blood cell and produces increased permeability, loss of potassium ions and shrinkage. This makes the cell more permeable or susceptible to mechanical injury, and at the same time causes an increased resistance to hypotonic saline solution. Lead not only causes hemolysis of the red cells, but also interferes with hemoglobin synthesis as shown by the large amounts of coproporphyrin type III which are excreted in the urine in cases of lead poisoning.

Case Reports

I shall report two cases in which the clinical features were typical of lead poisoning in children less than three years of age.

Case 1—A 30 month old girl had eaten paint from window sills for four months. Episodes of screaming had developed suddenly. They had occurred at any time during the day, and each one had lasted about 10 minutes. At the time these episodes had developed, she had begun to vomit four or five times a day. The vomiting had not been related to the ingestion of food. Constipation had been present for five months before she was admitted to the hospital.

Physical examination did not disclose any abnormalities. The erythrocyte count was

FIGURE 1. Increased density (lead line) at ends of radius and ulna in case 1. This is caused by concentration of lead at the growing ends of the shafts of long bones.

4,300,000, the leukocyte count 9500, and the value for the hemoglobin was 7 gm. per 100 cc. of blood. Examination of a blood smear revealed poikilocytosis and occasional basophilic stippling of the erythrocytes. Roentgenographic examination revealed increased density at the ends of the radius and ulna (figure 1). Urinalysis disclosed an increased excretion of coproporphyrin. A 24 hour specimen of urine contained 0.1 mg. of lead per liter, and the blood contained 133 μg. of lead per 100 cc. An electro-encephalogram showed that there was some slowing of the waves.

Sodium citrate was administered, and she was given a diet that was high in calcium and vitamin D. She improved slowly, and was dismissed from the hospital three weeks after her admission. The parents were instructed to bring the child to the outpatient clinic for further observation.

Case 2—A 22 month old girl had been known to chew on window sills and paint for five months. For two weeks before she was admitted to the hospital, she had vomited

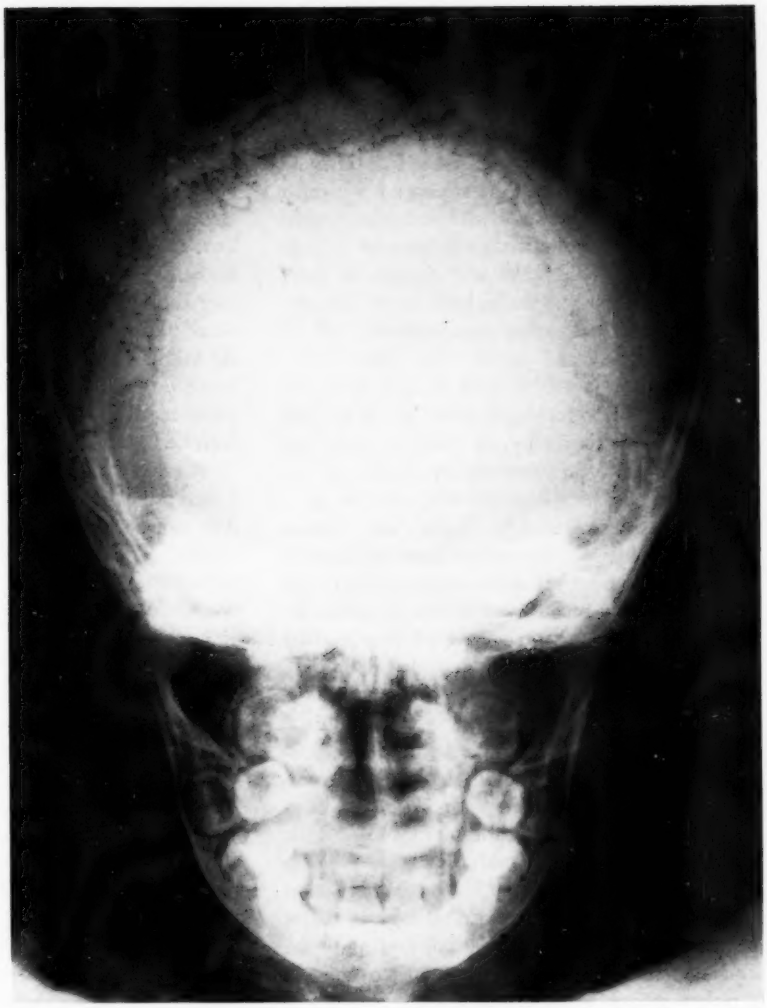


FIGURE 2. Separation of sagittal and coronal sutures (case 1) due to edema and cerebral pressure caused by lead encephalitis.

about 15 minutes before meals and had been irritable. She had been treated for tonsillitis and had been given an injection of penicillin. A clonic convulsion had occurred suddenly and had lasted 15 minutes.

When the child was examined in the emergency clinic, she had an internal strabismus of the left eye, and the optic disk of that eye was hyperemic. Macewen's sign was positive. The erythrocyte count was 3,800,000, the leukocyte count was 9100, and the value for the hemoglobin was 8.5 gm. per 100 cc. of blood. Examination of a blood smear revealed anisocytosis, poikilocytosis, and basophilic stippling of the erythrocytes. Roentgenographic examination of the long bones revealed a heavy metal deposit, and similar examination of the skull disclosed separation of the sagittal and coronal sutures (figure 2). The urinary excretion of coproporphyrin was increased. A 24 hour specimen of urine contained 0.09 mg. of lead per liter, and the blood contained 83 μg. of lead per 100 cc. An electro-encephalogram showed extensive slowing of the waves.

BAL (DIMERCAPROL®) was given every four hours intramuscularly as a 10 per cent solution in oil in doses of 4 mg. per kilogram of body weight, and administration was continued for 20 days. The child was given a diet high in calcium and vitamin D. The palsy of the sixth cranial nerve disappeared within a week. Within three weeks, roentgenographic examination revealed that the cranial sutures were closing. The child was dismissed from the hospital, but was to be brought to the outpatient clinic for further observation.

Diagnosis

The initial symptoms may be mild. Although the history may be characteristic, the symptoms may be so common that they do not cause the physician to suspect the presence of lead poisoning. The history always will disclose a pica for paint, but this may be hard to elicit because many parents think that it is a perfectly normal condition. The history almost invariably will reveal that constipation has been present for many months. This may have been quite intractable, and may have been treated in various ways. Since abdominal pain is a frequent symptom, the pain and constipation may be attributed to some gastrointestinal disturbance. The pain is generalized and colicky in nature, and palpation of the abdomen usually does not disclose any definite point of tenderness. If the constipation results in stools that are hard enough to cause rectal fissures, there will be blood in the stools, and this may cause the physician to suspect a polyp or a Meckel's diverticulum.

Vomiting occurs almost invariably. It may not have any relation to the ingestion of food, or it may occur in the course of each meal. The amount of vomitus usually is not large, and the vomiting may be somewhat projectile. It usually is not accompanied by pain, and it does not relieve the other symptoms. While vomiting may occur for several weeks or months, it almost always is a forerunner of the convulsion that is invariably associated with encephalitis.

In cases of chronic lead poisoning, severe symptoms such as convulsions, optic edema or atrophy, and paralysis of the peripheral nerves may not occur until the disease has been present for a long time, or they may occur suddenly in association with some secondary disturbance, such as an infection of the upper part of the respiratory tract. As a result, the symptoms may be attributed to the secondary disturbance. Any secondary disturbance such as acidosis will release a large amount of lead into the tissues and thus cause an exacerbation.

Pallor is a common symptom, and it is out of all proportion to the severity of the anemia. As might be expected from the gastrointestinal symptoms, anorexia occurs, and the child almost invariably loses weight or fails to gain weight.

The liver is slightly enlarged in some cases. Since the enlarged liver is not tender and does not cause any symptoms, it is easily overlooked. The increase in size probably is due to the storage and excretion of lead by the liver.

Examination of the blood will reveal a hypochromic microcytic anemia that is refractory to iron. In most cases, the value for the hemoglobin is less than 9 gm. per 100 cc. of blood, and the erythrocyte count is between 3,000,000 and 4,000,000. Basophilic stippling of the erythrocytes may be present, but it does not occur as constantly as is usually stated.

The concentration of lead in the blood is a very reliable guide to the presence of lead poisoning. If it is more than 0.06 mg. per 100 cc., it indicates the presence of lead poisoning or, at least, an increased exposure to lead. In most cases, the concentration of lead is more than 0.1 mg. per 100 cc. of blood.

When drawing blood for determining the concentration of lead, the syringe should be carefully deleaded by rinsing in 1 per cent nitric acid. It then should be thoroughly rinsed in distilled water.

The urine will be clear, and it sometimes may contain a few erythrocytes or leukocytes. In many cases, urinalysis may disclose a trace of sugar, or it even may reveal glycosuria grade 2 or 3 plus. The urine also will contain a trace of albumin, and albuminuria grade 2 or 3 plus may be present.

According to Byers, Maloof and Cushman,[1] the urinary excretion of lead is of great value in the diagnosis of lead poisoning. They said that the excretion of more than 80 μg. of lead in 24 hours always indicated the presence of lead poisoning in cases in which the patients were between six months and 14 years of age, that the excretion of 55 to 80 μg. always indicated more than the usual contact with lead and the possibility of lead poisoning, and that values less than 55 μg. rule out the condition except in cases in which patients who were desperately ill with lead poisoning were believed to have an inadequate renal blood flow.

Detection of the presence of porphyrinuria is of great value in the early diagnosis of lead poisoning. The results of studies by Maloof[2] in this country and by Shiels, Palmer, Cornish and Kearley[3] in Australia indicate that it is present in every case of lead poisoning. It occasionally occurs after administration of the sulfonamide drugs, and it also occurs in cases of poisoning by other heavy metals and in cases of cirrhosis of the liver, chronic alcoholism, aplastic anemia, poliomyelitis and Hodgkin's disease. Testing the urine for the presence of porphyrin is a simple screening test for lead poisoning that can be performed in any doctor's office in five minutes.

The test is performed in the following manner: Take 5 cc. of urine in a test tube and acidify with 2 or 3 drops of glacial acetic acid. Add 5 cc. of ether, and shake the tube vigorously. Allow the layers to separate well, and examine under a Wood's lamp for one minute in a darkroom. A salmon-pink fluorescence in the ether layer indicates the presence of porphyrin.

The cerebrospinal fluid is clear and usually contains few, if any, cells. Pandy's test will disclose an abnormal amount of globulin, and the concentration of protein usually is more than 100 mg. per 100 cc. Giannattasio, Bedo and Pirozzi[4] said that the presence of lead poisoning should be suspected if the cerebrospinal fluid is crystal clear, if the result of Pandy's test is positive, and if the cell count is normal or almost normal.

When lead is absorbed in children who are growing, it is deposited at the growing ends of the shafts of the long bones and in the growing margins of the flat bones. This forms a dense opaque band or line which is called the lead line and can be demonstrated roentgenographically. Similar lines or bands may be observed in cases of rapidly healing rickets, or may be caused by the deposit of any heavy metal such as bismuth. This finding alone, therefore, cannot be accepted as evidence of lead poisoning. Recently, Keefer and Mokrohisky[5] have called attention again to the fact that roentgenographic examination may disclose dense zones at the anterior ends of the ribs and a sharp line of demarcation between the bone and cartilage at the costochondral junction.

The diagnosis of lead poisoning should be considered in all cases in which children who have a pica for paint complain of constipation, abdominal pain and vomiting. It should be given first consideration in cases in which children have an isolated convulsion that is not associated with fever or other physical signs. In such instances, a simple test for porphyrinuria will indicate the possibility of lead poisoning. If porphyrin is present in the urine, the blood should be searched for basophilic stippling, and a roentgenogram of the long bones should be made in order to determine whether or not a lead line is present. An abnormal quantity of lead in the blood or urine will confirm the diagnosis.

Lead poisoning must be distinguished from such gastrointestinal disorders as diverticulum, polyps and intussusception, which cause colic and constipation. With the exception of these symptoms, none of these disorders have anything in common with lead poisoning, and their possible presence can be eliminated by roentgenologic examination of the intestinal tract with barium. In cases in which paralysis of the peripheral nerves is present, the possible presence of poliomyelitis, diphtheria, Guillain-Barré syndrome and lesions of the spinal cord must be considered. In all of these conditions, the blood, urine and spinal fluid findings are quite different from those of lead poisoning, with the exception that porphyrinuria occasionally has been observed in cases of poliomyelitis. When lead encephalopathy is

present, the clinical manifestations as well as the cytologic changes in the cerebrospinal fluid may simulate those encountered in cases of acute meningitis, tuberculous meningitis, encephalitis of various forms, and brain tumor or abscess. The cell count in the cerebrospinal fluid is of diagnostic value. In cases of uncomplicated lead encephalitis, the cell count is nearly normal or only slightly increased. Sickle cell anemia and diabetic coma may offer some problems, but examination of the blood and urine should easily distinguish them from lead poisoning.

Treatment

Since lead poisoning is preventable, prophylactic treatment is most important. Successful prevention depends on the education of the general public, particularly parents, in the likely sources of lead poisoning and its dangers. Manufacturers of cribs and toys have learned these facts and do not use lead paints on their merchandise. Parents and other persons have yet to learn this lesson.

In cases in which encephalitis has not been present, treatment for years has been directed toward the rapid removal of lead from the circulation and its deposition in the bones. This treatment has consisted of a diet that is high in calcium and phosphorus, for example, a quart of milk a day, and the administration of large doses of vitamin D.

If encephalitis is present and convulsions occur, these therapeutic measures must be supplemented by the administration of sedatives, and by the oral administration of calcium gluconate, four times a day, unless vomiting is present. If vomiting occurs, a 10 per cent solution of calcium gluconate may be administered intravenously. The dose of this solution depends on the age of the child. Convulsions may be controlled by administering a 25 per cent solution of magnesium sulfate. This solution is administered every six hours intramuscularly in doses of 0.2 cc. per kilogram of body weight. Its administration is discontinued after six doses have been given.

Deleading may be accomplished by the same measures that cause decalcification, namely, the administration of parathyroid extract and acid forming salts. Sodium citrate has been used most often for this purpose. It is given orally in cherry syrup, three times a day, in doses of 1 to 2 gm. Such deleading procedures are not free from danger since the amounts of lead which reappear in the circulation may be sufficient to cause cerebral symptoms. At present, these procedures are not generally used since it has been observed that deleading gradually will occur spontaneously once the source of the lead has been removed.

The presence of lead in the bones may at any time be a source of danger, particularly if an acute infection develops. For this reason, attempts have been made to remove lead by some means that will not precipitate an acute exacerbation. Ennis and Harrison[6] used BAL in the treatment of lead encephalopathy in 1950, and they concluded that it lowered the mortality rate and reduced the severity of the residua of severe lead encephalopathy.

In 1952, Giannattasio, Bedo and Pirozzi[4] reported the results obtained by the administration of BAL in two cases of lead poisoning in which the patients were two and three years of age, respectively. Four milligrams of BAL per kilogram of body weight was administered every four hours around the clock for 10 days. The end results in these cases were better than those in three comparable cases in which the patients were treated in the usual manner. In another article, Giannattasio, Bedo, Pirozzi and Jennings[7] said that BAL was nontoxic when given in safe doses. If administered in large doses, BAL occasionally may cause toxic reactions such as nausea, headache, vomiting, abdominal pain and flushing of the face. If a reaction occurs, it may be relieved by the oral administration of 5 or 6 mg. of ephedrine sulfate to a two year old child or by the intramuscular administration of 0.1 or 0.2 cc. of 25 mg. ephedrine sulfate in 1 cc. of sterile water.

Another approach to the treatment of lead poisoning has been by the use of chelating agents. These substances form a lead complex by exchanging calcium for lead to form a tight chelate which can circulate in the blood without any apparent toxicity. Edathamil calcium-disodium (calcium-disodium VERSENATE®;

calcium disodium ethylene diaminetetra-acetic acid; Ca EDTA) is such an agent, and it has been used by Byers and Maloof[8] in amounts of 1 gm. per 15 kg. of body weight divided into two doses and administered intravenously in 250 cc. of a 5 per cent solution of dextrose. Each dose is administered over a period of one or two hours. They used this treatment for three days, and then discontinued the use of the drug for three days.

The maximal total dose of this drug should not exceed 5 gm. per 30 pounds of body weight, and it should be given in divided doses. If the drug is administered intravenously, not more than 0.5 gm. per 30 pounds of body weight should be given in one hour. It should not be administered for more than 10 days, and the maximal total dose administered during this period should not exceed 7.5 gm. per 30 pounds of body weight. I have had no difficulty in cases in which I have administered this drug, and its administration would appear to be a very safe and efficient method of deleading, especially in cases in which convulsions are present.

Addendum

Bradley and Powell[9] have used oral calcium EDTA in the treatment of chronic lead poisoning. This was given in dosages of 75 mg. per kilogram of weight in divided doses at six hour intervals for nine days. It was well tolerated and brought about disappearance of anorexia and irritability. However, they suggest that, in acute lead intoxication and in lead encephalopathy where it is necessary to obtain a rapid excretion of lead, intravenous calcium EDTA be used.

Comment

Although it generally is believed that children who have lead poisoning usually recover without any residua if the source of the lead is removed, this is not true. Manifestations of encephalitis develop in approximately half of the cases, and the mortality rate is about 25 per cent in cases in which such manifestations develop. Permanent neurologic sequelae occur in at least a third of the cases in which the patients recover from the encephalitic phase of the disease. The subsequent mental development should be watched closely.

Every effort should be made to diagnose and treat lead poisoning as soon as possible. Lead poisoning in children can be prevented by prophylactic measures. This should be realized by physicians, and parents should be convinced of the serious consequences of the continuous ingestion of lead so that it may be avoided.

REFERENCES

1. Byers, R. K., Maloof, C. A. and Cushman, M.: Urinary excretion of lead in children; diagnostic application. Am. J. Dis. Child. 87:548 (May) 1954.
2. Maloof, C. A.: Role of porphyrins in occupational disease. Arch. Indust. Hyg. & Occup. Med. 1:296 (March) 1950.
3. Shiels, D. O., Palmer, G. R., Cornish, P. E. and Kearley, E. J.: Porphyrinuria in persons exposed to lead hazards. Australian M. J. 2:171 (August 1) 1953.
4. Giannattasio, R. C., Bedo, A. V. and Pirozzi, M. J.: Lead poisoning; observations in 14 cases. Am. J. Dis. Child. 84:316 (September) 1952.
5. Keefer, G. P. and Mokrohisky, J. F.: Lead poisoning; roentgenograms of the chest as an aid in diagnosis. J. Pediat. 43:146 (August) 1953.
6. Ennis, J. M. and Harrison, H. E.: Treatment of lead encephalopathy with BAL. Pediatrics 5:853 (May) 1950.
7. Giannattasio, R. C., Pirozzi, M. J., Bedo, A. V. and Jennings, K. G.: BAL therapy in chronic lead poisoning. Pediatrics 10:603 (November) 1952.
8. Byers, R. K. and Maloof, C. A.: Edathamil calcium-disodium (versenate) in treatment of lead poisoning in children. Am. J. Dis. Child. 87:559 (May) 1954.
9. Bradley, J. E. and Powell, A. M.: Oral calcium EDTA in lead intoxication of children. J. Pediat. 45:297 (September) 1954.

Problems in the Surgical Care of Infants and Children

CLIFFORD D. BENSON AND PRESCOTT JORDAN, JR.*

Wayne University College of Medicine, Detroit

CLIFFORD D. BENSON

WITHIN the past 15 years the advance in the surgical treatment of infants and children has kept pace with that in many other surgical fields. Not a small part of this advance has been the improved understanding of the special problems presented by this group of patients. These problems which are presented daily in both the preoperative and the postoperative care of the patient were until a few years ago handled inefficiently because of the lack of understanding of the uniqueness of this group of surgical patients. One cannot gloss lightly over the fact that the improvement in anesthesiology as well as in the medical treatment of these patients has made the successful accomplishment of many difficult surgical procedures possible.

*Surgical Service, Children's Hospital of Michigan; Wayne University College of Medicine, Detroit, Michigan.

Physiologic Considerations

The most important physiologic consideration in treatment of these patients is their immaturity. The physiologic balance in a young infant has not had time to develop. Premature infants are much less able to cope with their environment and the stresses that are placed on them than are even full-term children. Pediatricians have recognized for some time that infants have an instability in temperature regulation, a low respiratory and cardiac reserve, and a relatively low concentration of protein in the plasma.

Immaturity of the renal function makes the correction and the maintenance of the electrolytic and fluid balance in these patients a most difficult and critical problem. Since renal maturation is not achieved until an infant attains a weight of 2500 gm., electrolytic balance is easily thrown into imbalance by relatively small losses of body fluids. This immaturity is demonstrated histologically by a nephrogenic zone in which glomeruli are developing. The low concentration of protein in the plasma, which results in a low plasma osmotic pres-

sure, and the renal immaturity make premature and full-term infants far more susceptible to the development of edema. Renal function as gauged by urea clearance is distinctly inferior to that of adults, and not until the second year does a child's function reach the so-called normal adult level.

The weight of a normal full-term infant is approximately 5 per cent of that of an average adult, but the body surface is 50 per cent of that of an adult. In the case of a premature infant, this disproportion is even greater. Approximately 75 per cent of the weight of an infant's body is attributable to water, whereas water accounts for approximately 60 per cent of the weight of an adult. During the first two years of life, the relative amount of water in the body gradually approaches that in the body of an adult. Thereafter, the difference is small.

The premature infant has a limited peripheral vasomotor control, and the skin has practically no insulating fat. Thus he must work harder to maintain his body temperature in order to survive. Owing to the high rate of heat production, a greater respiratory effort is necessary at the expense of his respiratory reserve. The full-term infant has only a limited respiratory reserve, and the premature infant has almost none. Respiratory difficulty will become evident immediately if an overwhelming infection such as pneumonia, or another condition such as atelectasis, diaphragmatic hernia or even abdominal distention, which also harrasses the respiratory tract, should occur. The resulting demand for increased energy will require an increased cardiac output at the expense of the reserve. Combined with the poor vasomotor control, this will tend to make the infant susceptible to minute alterations in blood volume for which he cannot easily compensate.

Since the newborn infant is very susceptible to infection, any rough handling or poor surgical technic, with the resultant friability of tissues, may lead to severe, incapacitating local infection. The gastrointestinal mucosa of premature infants and of young infants who were born at full-term is particularly delicate and must, therefore, be handled with the utmost care in performing any type of intestinal anastomosis. The possible occurrence in the normal premature infant of a transient hypothrombinemia two or three days after birth, even though at birth the coagulation time was found to be normal, must always be considered when it is anticipated that an operation will be performed.

The newborn infant will stand an operation of great magnitude if the foregoing factors are considered by the surgeon. Shock can be greatly reduced by good hemostasis, by keeping the baby warm while on the operating table, and by the judicious use of blood and plasma to support the child during the operation. It is generally agreed that no child is too small or too young for operation today. The nature of the emergency should be the guiding factor in determining whether or not one should operate. Many congenital lesions such as obstructive lesions of the gastrointestinal tract, diaphragmatic hernia with marked respiratory embarrassment, omphalocele, and teratoma of the scrotum demand immediate operation. With the aids outlined above and with an understanding of the problem presented by these special patients, operation can be done with a satisfactory mortality rate.

Fluid Requirements of Infants

In practically all cases in which operations are performed on infants, blood and fluids must be administered intravenously before and after the operation. Since infants have a limited cardiac reserve and are very susceptible to edema, fluid must be given slowly by the drip method. It is generally agreed that more harm is done by giving too much fluid than by keeping the patients on the dry side. Since the immature kidneys have a very limited ability to excrete electrolytes, excessive amounts of these substances should be administered only rarely.

No more than 35 or 50 cc. of fluid per pound of body weight should be administered intravenously in 24 hours to an infant who is in the first stage of life and who has not taken anything by mouth. Fluids are best administered slowly by the drip method, through a No. 23 needle, at a rate of 10 drops per

minute. In some institutions, fluids are given in divided doses. If fluids are administered too rapidly, they may overload the cardiovascular system. A 10 per cent solution of dextrose should not be administered intravenously at a rate greater than 1 drop per minute per pound of body weight. If it is administered more rapidly, the body will not be able to metabolize and store the dextrose, and an undesirable loss of dextrose as well as water and electrolytes will occur in the increased excretion of urine that will result from the rapid administration of the solution of dextrose.

If a solution of amino acids is administered intravenously at a rate of more than 1½ drops per pound of body weight per minute, it may cause a speed reaction, which is manifested by fever, flushing, nausea and vomiting, and an increased amount of fluid may be lost.

To provide fluids and some calories, we prefer the intravenous administration of a 10 per cent solution of dextrose in water. Rarely, this is mixed with a small amount of physiologic saline solution. The fluids also can include plasma if the concentration of total plasma protein is low, or 5 to 10 cc. of whole blood per pound of body weight can be given if the value for the hemoglobin is low. The amount of fluid that is advocated here admittedly is less than the amount required to keep the fluid balance of an infant in the ideal state, but our experience indicates that a larger amount courts the danger of overhydration. Many authors, particularly Snyder, Snyder and Chaffin,[1] have advocated the use of even smaller amounts. Clinical judgment is the most reliable guide to the requirement for fluids. This can be determined by noting the turgor of the skin, dryness of the mouth, the amount of weight that is lost or gained, frequency of micturition, and the amount of urine that is voided.

Gross[2] has said that the kidneys of young infants cannot excrete large amounts of sodium chloride. Physiologic saline solution is given only in rare instances, e.g., in cases in which continuous suction is used. When minimal amounts of fluid are lost by suction, only a sixth of the total amount of fluid required can be given in the form of physiologic saline solution. This rule has been broken occasionally but, when it has been, the infants have been observed very carefully. As soon as the infant is able to tolerate the ingestion of fluids and milk by mouth, any chemical imbalance will be corrected very rapidly.

Routine biochemical tests are not necessary, but are very important if the oral intake is delayed, if the clinical course is complicated, or if edema or marked dehydration is present. By using microchemical methods, a Gamblegram can be made with 4 or 5 cc. of heparinized blood. Formerly, 10 cc. of blood was necessary for chemical analysis. Since the removal of 10 cc. of blood from a premature infant corresponds to the removal of 200 or 300 cc. of blood from an adult, it obviously is a risky procedure if the infant is critically ill.

In determining the postoperative fluid requirements of premature infants and infants who were born at full term, it is well to remember that the concentration of protein in their serum is low. When this is coupled with starvation and the tendency to edema, it is important to keep the concentration of plasma protein at a satisfactory level for a week after an operation. It has been our policy to administer a small amount of plasma each day. The amount that is given should not exceed 10 cc. per pound of body weight. If the erythrocyte count is less than 4,000,000 on any day, whole blood is administered instead of plasma on that day.

The oral ingestion of fluids usually can be started on the third or fourth day after the surgical correction of an underlying pathologic condition such as intestinal obstruction, and the fluid requirements of the infant can be met easily in this manner.

The normal value for the carbon dioxide-combining power of the plasma of premature infants is on the acid side, that is, 13 to 17 mEq. per liter, while that for the carbon dioxide-combining power of the plasma of a full-term infant or one who is several months old is 20 to 22 mEq. per liter. The normal value for the serum sodium of infants is 138 to 144 mEq. per liter, and that for the serum potassium is 4 to 7 mEq. per liter.

If the carbon dioxide-combining power of

the plasma is 30 mEq. or more per liter, a one-sixth molar solution of ammonium chloride is administered subcutaneously. Administration of 2 cc. of this solution per pound of body weight will reduce the carbon dioxide-combining power of the plasma 1 mEq. per liter. The use of this solution has been of inestimable value especially in cases of pyloric stenosis in which severe alkalosis was present when the infants were admitted to the hospital. In former years, only physiologic saline solution was administered to correct the altered chemical composition of the blood, and the infants frequently became edematous before operation was performed.

We have found that continuous pooling of chlorides occurs in the stomach in cases of severe pyloric obstruction. This prevents full correction of the alkalosis. Further correction is not possible until the mechanical obstruction has been relieved by a Fredet-Ramstedt operation.

Fluid Requirements of Older Children

For practical purposes, the basic requirements for the intravenous administration of fluids, both preoperatively and postoperatively, for a 24 hour period, are as follows: for a child three to five years old, 45 to 50 cc. per pound of body weight; for a child five to eight years old, 35 to 40 cc. per pound; for a child 8 to 12 years old, 30 to 35 cc. per pound. These requirements are met by the intravenous administration of a 10 per cent solution of dextrose in water and physiologic saline solution, but, if a considerable amount of electrolytes, chiefly sodium and chloride, has not been lost, only a sixth of the total quantity of fluid is given in the form of physiologic saline solution. If an excessive amount of electrolytes has been lost, the amount of physiologic saline solution in the mixture can be increased to a third of the total amount given. This will meet the requirements in an average case in which an operation is performed. If microchemical analysis reveals the presence of a refractory alkalosis, a one-sixth molar solution of ammonium chloride can be administered subcutaneously as recommended for infants.

If intestinal fluids have been lost by vomiting, by suction drainage for three or four days, by diarrhea, or through an ileac stoma, a potassium deficiency may ensue. In cases in which such a deficiency occurs, we add potassium chloride to the solution that is to be administered intravenously. The amount of potassium chloride should not exceed 10 mEq. per liter of solution. This, we admit, is on the low side for full correction of the deficiency, but it has been found to be safe and effective.

Decompression of the Intestine

The gastric contents should be aspirated before an abdominal operation is performed. In the case of a premature infant, this can be accomplished by the insertion of a No. 8 urethral catheter. Postoperatively, the gastric contents can be aspirated intermittently with the same type of catheter. If a Levin tube is left in place, it is likely to cause swelling of the hypopharynx and epligottis which, in turn, may lead to laryngeal obstruction.

In infants who were born at full term, we use a Levin tube with a small caliber, and we never have experienced any difficulty in cases in which the tube has been withdrawn within two or three days. The Levin tube and the Wangensteen suction apparatus are satisfactory in most cases in which abdominal operations are performed on infants. The tube is left in place until the aspirated material is clear and free of bile. When certain lesions are present, complete surgical decompression of the involved segment of the intestine can be achieved by removing all gas and liquid at the time of the operation.

Distention can be prevented by keeping a Levin tube in place postoperatively so that swallowed air can be aspirated. This is important, especially in cases in which an intestinal anastomosis has been performed. The use of a long tube is feasible in children if intestinal decompression is deemed necessary. In our experience, this rarely has been necessary except in some older children in whom peritonitis has caused an extensive ileus or in whom a localized exudative process has caused persistent mechanical obstruction of the intestine. During the last seven years, the long tube has been used for these indications in only 6 of

more than 400 cases in which operations have been performed on infants and children who had perforated appendixes and peritonitis.

Oxygen Therapy

Pediatric tents and incubators ordinarily have limitations which permit a maximal oxygen concentration of only 60 per cent in the inspired air. Our only indications for increasing the oxygen content of the inspired air are as follows: (1) when the oxygen saturation of the hemoglobin is less than 95 per cent, and (2) when the normal oxygen saturation of the inspired air is being maintained only by increased respiratory effort. This eventually causes fatigue. A partial increase of the oxygen pressure in the alveoli will permit the oxygen saturation of the hemoglobin to remain normal. The first indication is one type of hypoxia, and the second might be termed compensated hypoxia. Oxygen is beneficial when hypoxia is due to one of the following causes: (1) a decrease in the amount of oxygen in the inspired air; (2) a decrease in the air exchange due to obstruction of the airway or impairment of diaphragmatic or intercostal power, and (3) a decrease in the absorption of oxygen through the pulmonary alveoli due to atelectasis, pneumonitis or pulmonary edema.

Oxygen is used almost routinely after all surgical operations on newborn infants, and especially after operations on premature infants in whom the respiratory reserve is practically nil. Since most premature infants need an oxygen concentration of 35 to 45 per cent in the inspired air, the incubator should deliver about 3 or 4 liters of oxygen per minute. Premature infants who are very ill require 8 liters of oxygen per minute. The Armstrong incubator fulfills this need very well. It also conserves body heat, provides adequate humidity, and permits the baby to be isolated from other patients and from attendants. The ISOLETTE® probably is the ideal type of incubator for a premature infant. When this is used, one can provide oxygen and adequate heat and humidity, and the infant will be disturbed only slightly by treatments. Since it costs about six cents an hour to administer oxygen, it should not ever be wasted.

Oxygen is of inestimable value in cases in which intestinal distention develops in infants and small children and cannot be relieved by decompression because a tube cannot be inserted to the proper level.

Vitamins are administered parenterally to all infants before and after operation. The best preparation to use is a water-miscible one. It is available as prepared by many drug companies. Each 0.6 cc. (0.3 to 0.6 cc. is daily dosage for infants) contains not less than

Vitamin A	5000 units
Vitamin D	1000 units
Thiamine chloride	1.0 mg.
Riboflavin	0.4 mg.
Ascorbic acid	50.0 mg.
Niacinamide	2.0 mg.

Vitamin K is administered intramuscularly in the dosage of 1 cc. of SYNKAMIN® while the other vitamins can be given by mouth, either in the infant's formula or in any fluids which the child prefers.

Drug Therapy

Table 1 shows the premedication that has been found very satisfactory by our anesthetists. If additional sedation is required, 2 mg.

TABLE 1

PREMEDICATION FOR INFANTS AND CHILDREN

AGE	MORPHINE*	SCOPOLAMINE*
Less than 6 mo.	None	None
6 mo. to 1 yr.	None	1/900 gr.
1 to 2 yr.	None	1/600 gr.
2 to 4 yr.	1/64 gr.	1/400 gr.
4 to 6 yr.	1/32 gr.	1/400 gr.
6 to 8 yr.	1/24 gr.	1/300 gr.
8 to 10 yr.	1/18 gr.	1/300 gr.
10 to 12 yr.	1/16 gr.	1/200 gr.
12 to 14 yr.	1/12 gr.	1/200 gr.

*The respective doses are administered subcutaneously.

of a barbiturate per pound of body weight is administered intramuscularly to infants and children. Small infants can have pain, and it may cause fatigue. Small doses of barbiturates will give these patients relief and rest.

We administer penicillin and sulfadiazine

routinely, particularly to premature and full-term infants, before and after operation. A half or ¾ gr., intravenously, as the sodium salt, or orally, of sulfadiazine per pound of body weight is administered in 24 hours.

Thrush is a peculiar complication that is likely to occur in cases in which antibiotics are being administered to infants. The antibiotics suppress the microorganisms that ordinarily are antagonistic to *Candida albicans*. If this complication should occur, the administration of antibiotics should be discontinued immediately.

Conclusions

1. Newborn babies and infants present physiologic problems which make them special patients when any surgical procedure is contemplated, and they cannot be considered as small adults.

2. Intravenous administration of excessive amounts of fluids can lead to serious complications and even may cause death.

3. To meet the needs of this special group of patients, well-trained and interested nurses and house physicians are necessary.

4. Surgeons now can carry out surgical procedures on newborn infants and young children with a reasonable mortality rate if they are cognizant of the special needs of these patients.

5. Because of uncontrollable factors such as serious coexisting anomalies, one must accept a minimal morbidity and mortality rate in infant surgery.

REFERENCES

1. Snyder, W. H., Snyder, M. H. and Chaffin, L.: Advances in surgery of the newborn. Arch. Surg. 68:546 (April) 1954.
2. Gross, R. E.: Surgery of Infancy and Childhood. Philadelphia, W. B. Saunders Company, 1953, p. 20.

BOOKS RECEIVED

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews and additional listings will be found in this issue starting on page A-116.

Treatment of Acute Poliomyelitis. By William A. Spencer, M.D., Medical Director, Southwestern Poliomyelitis Respiratory Center, Houston, Texas, with 22 contributors. Ed. 2. 134 pages. 1954, Charles C Thomas, Springfield, Illinois. $3.75.

Cultural Difference and Medical Care. By Lyle Saunders, Associate Professor of Preventive Medicine and Public Health (Sociology), University of Colorado School of Medicine, Denver, Colorado. 317 pages. 1954, Russell Sage Foundation, New York. $4.50.

Pediatric Diagnosis. By Morris Green, M.D., Assistant Professor of Pediatrics, and Julius B. Richmond, M.D., Professor and Chairman of the Department of Pediatrics, State University of New York College of Medicine, Syracuse. 436 pages. 1954, W. B. Saunders Company, Philadelphia and London. $10.00.

The Human Brain in Sagittal Section. By Marcus Singer, Ph.D., Professor of Zoology, Cornell University, Ithaca, and Paul I. Yakovlev, M.D., Assistant Clinical Professor, Department of Neurology, Harvard Medical School, Boston. 81 pages, illustrated. 1954, Charles C Thomas, Springfield, Illinois. $7.75 (nonflexible binding) and $6.25 (flexible).

Standard Values in Nutrition and Metabolism. Edited by Errett C. Albritton, M.D., Fry Professor of Physiology, The George Washington University, Washington, D.C. 380 pages. 1954, W. B. Saunders Company, Philadelphia and London. $6.50.

Diagnostic Laboratory Hematology. By George E. Cartwright, M.D., Associate Professor of Medicine, University of Utah College of Medicine, Salt Lake City. 104 pages, illustrated. 1954, Grune & Stratton, Inc., New York and London. $3.00.

The Distribution of the Human Blood Groups. By A. E. Mourant, M.A., Director, Medical Research Council Blood Group Reference Laboratory, The Lister Institute of Preventive Medicine, London. 438 pages. 1954, Charles C Thomas, Springfield, Illinois. $8.75.

Prerequisites of Good Teaching & Other Essays. By Ernest Sachs, M.D., Research Associate in Surgery and Medical History, Yale University School of Medicine, New Haven, Connecticut. 118 pages. 1954, The Shoe String Press, Hamden, Connecticut. $2.50.

Antibiotics and Antibiotic Therapy. By Allen E. Hussar, M.D., Chief of Medical Service, Franklin Delano Roosevelt Veterans Administration Hospital, Montrose, New York, and Howard L. Holley, M.D., Associate Professor of Medicine, Medical College of Alabama, Birmingham. 475 pages. 1954, The Macmillan Company, New York. $6.00.

Benign Diseases of the Breast

ROBERT L. SCHMITZ*

Stritch School of Medicine of Loyola University, Chicago

BENIGN diseases of the breast may be divided into four groups: (1) developmental, (2) hormonal, (3) inflammatory and (4) neoplastic. The various conditions included in these groups, in order of their discussion in this article, are listed in table 1.

ROBERT L. SCHMITZ

Developmental Anomalies

Anomalies of location and number. Polythelia and polymastia—Polythelia (supernumerary nipples) and polymastia (supernumerary breasts) (figure 1a, b and c) may be found anywhere along the course of the milk line. In addition, they have been reported on the face, ear, neck, arm, thigh and buttocks (Geschickter). How mammary tissue arrives in these latter locations is not known.

Usually, ectopic nipples require no treatment unless their location makes surgical removal desirable for cosmetic reasons. Ectopic breast tissue, especially in the axilla, may become quite tender from lactation or chronic cystic mastitis or may be the seat of benign or malignant neoplastic change, and for these reasons excision of the tissue is advisable.

Anomalies of size. Amastia—Rarely, the progressive atrophy of the milk line during embryonic life may extend through the pectoral region so that amastia, or total absence of the breasts, occurs.

Hypomastia—Not infrequently, mammary development is relatively inadequate, especially as far as the patient's own wishes go, but unless the hypomastia is associated with generalized hormonal deficiency such as hypogonadism, it is unwise to attempt stimulation by endocrine therapy.

Hypermastia—Most commonly, the anomaly of breast size for which advice is sought is mammary hypertrophy, hypermastia. The breasts of newborn infants of either sex may be visibly and palpably enlarged and may even secrete a few drops of milklike fluid (figure 2a). It is presumed in such cases that the mammary glands of the infant have been stimulated by the hormones of late pregnancy in

*Assistant Clinical Professor of Surgery, Stritch School of Medicine of Loyola University, Chicago, Illinois.

TABLE 1

1. *Developmental anomalies*
   - Anomalies of location and number
     - Polythelia
     - Polymastia
   - Anomalies of size
     - Amastia
     - Hypomastia
     - Hypermastia
       - Infantile
       - Virginal
       - Gravid
       - Gynecomastia
2. *Hormonal disorders*
   - Chronic cystic mastitis
     - Mastodynia
     - Adenosis
     - Fibrocystic disease
   - Effects of pregnancy and lactation
     - Abnormalities of lactation
     - Painful engorgement
     - Galactorrhea
     - Galactocele
3. *Inflammatory lesions*
   - Nonspecific infections
     - Acute mastitis
     - Chronic mastitis
     - Terminal duct infection
     - Infection of Montgomery's follicles
   - Specific infections
   - Fat necrosis
4. *Benign neoplasms*
   - Nonindigenous tumors
   - Fibroadenomas
   - Intraductal papillomas

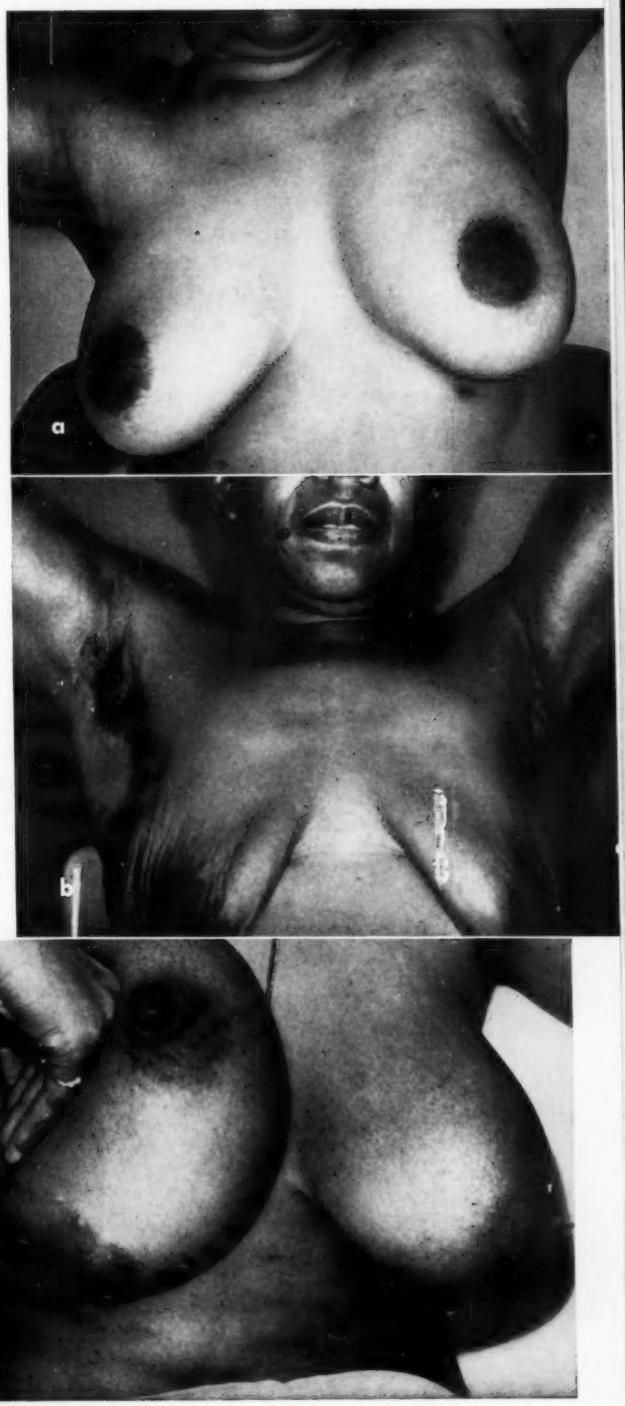


FIGURE 1. Polythelia and polymastia.
a. Supernumerary nipples below the breasts; accessory breast tissue in the axilla.
b. Accessory breast tissue in both axillae.
c. Complete duplication of breast.

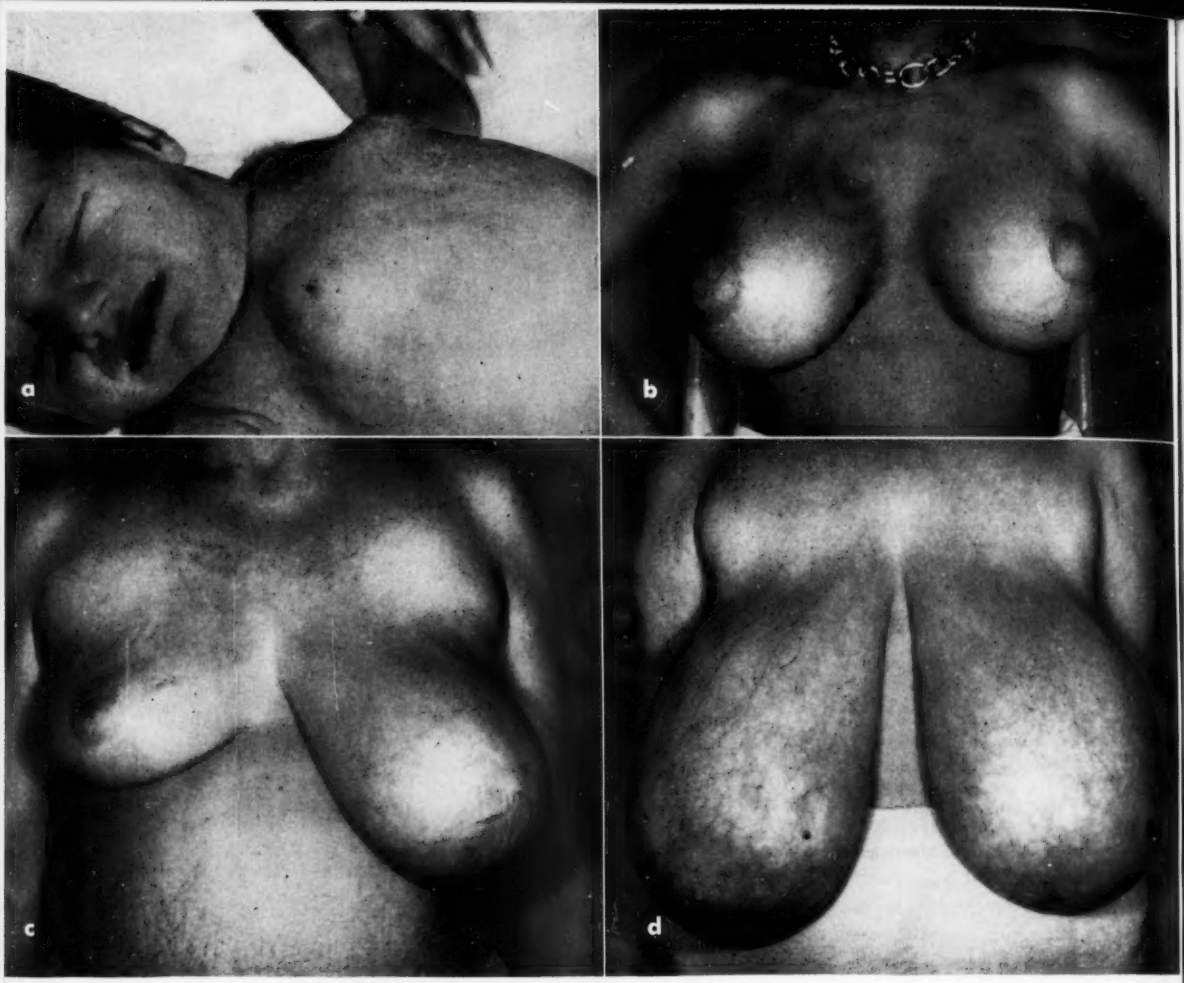
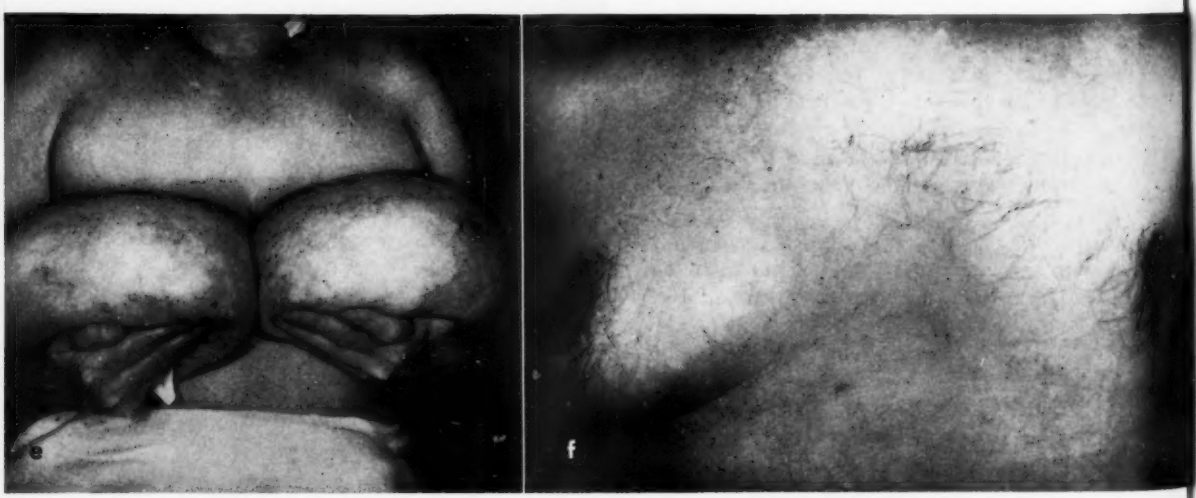


FIGURE 2. Hypertrophy of the breast. a. Newborn. b. Bilateral virginal hypertrophy in a 14 year old girl. c. Unilateral virginal hypertrophy. d. Gravid hypertrophy. e. Gravid hypertrophy, same as (d). f. Gynecomastia.



the mother. No treatment is indicated. In a few days the process recedes.

Precocious mammary development between birth and puberty is part of a generalized endocrine disturbance from such lesions as feminizing tumors of the ovary, tumors or hyperplasia of the adrenal cortex, and lesions of the floor of the third ventricle or hypothalamus.

Early in puberty, in males or females, there may be unilateral enlargement of a breast, "early ripening," to a degree that alarms the parents. Balanced growth almost invariably follows, although an occasional case goes on to unilateral virginal hypertrophy.

In some adolescent females a unilateral or bilateral enlargement of the breasts occurs called virginal hypertrophy (figure 2b and c). The mechanism of this enlargement is not known, but it may reach a degree necessitating surgical reduction in size of the involved breast or breasts. A similar condition, gravid hypertrophy, is seen occasionally during pregnancy and lactation. The breasts do not undergo normal postlactational involution and, again, plastic surgery may be indicated (figure 2d and e).

Hypertrophy of the breast in the male, gynecomastia (figure 2f), may involve one or both breasts and usually comes on idiopathically at puberty although it is seen idiopathically in adults and in cases of tumor of the testis, adrenal cortex or hypophysis, hermaphrodism, hepatic cirrhosis and chronic malnutrition, and following estrogen therapy. Microscopically, tissue from gynecomastia resembles that of the normal female breast although occasionally a good deal of fibrous tissue and nodularity are present and the term adenofibrosis is used. Treatment is usually not necessary. Hormonal therapy accomplishes little and always runs the risk of side effects. When cosmetic deformity is of sufficient degree, excision of the breast is done with preservation of the nipple.

Hormonal Disorders

Chronic cystic mastitis—This is an inaccurate descriptive term but the one most often applied to a variety of pathologic changes in the breast which are also termed mammary dysplasia, mastopathy, mazoplasia, lobular hyperplasia and Schimmelbusch's disease.

Clinically, three principal types of cystic mastitis can be identified: (1) mastodynia, characterized by painful areas of increased density without any distinct masses; (2) adenosis, in which the involved portion of the breast is nodular, granular or grapey to palpation, and (3) fibrocystic disease, in which cysts of varying size appear with relatively normal stroma. In general, these various types tend to be mixed to some degree in any given patient.

The most popular theory for the etiology of chronic cystic mastitis pictures an excessive estrogen phase in the ovary with stimulation of the breast elements and a correspondingly deficient progesterone phase so that the stimulated tissues do not completely regress. Gradually, hyperplasia of the ducts and the acini occurs, and then fibrosis about these structures from stromal stimulation. Finally, secretory changes take place and the typical blue-domed cysts form. The duct epithelium begins to pile up, and intraductal and intracystic papillomas may be an end product of this process. It is easy to see why there has been so much effort to relate these hormonal disturbances to the occurrence of carcinoma. Incidentally, that relationship has not yet been established.

This disease occurs during the menacme in women who tend to have menstrual irregularities—mastodynia usually in early adult life, adenosis in mid-adult life, and cystic disease in the menopausal period—but exceptions are common. The breasts are dense, lumpy or even plaquelike, painful and tender, especially around the time of the menses. Not infrequently the distress becomes constant and may continue for years. Nipple discharge is seen in only 10 per cent of the cases and is rarely bloody. The disease disappears during pregnancy and lactation and tends not to recur, especially in women who have multiple pregnancies.

The treatment of chronic cystic mastitis is mainly conservative. Reassurance of the patient is always important, as many of them

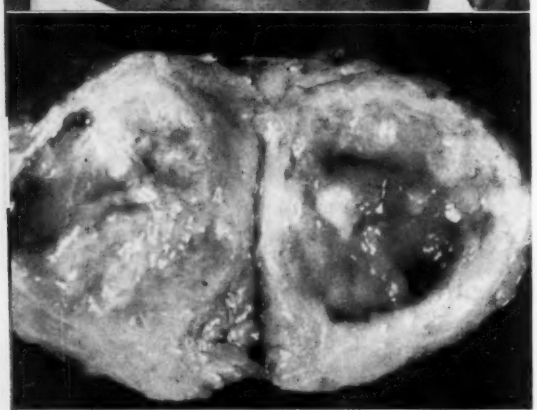
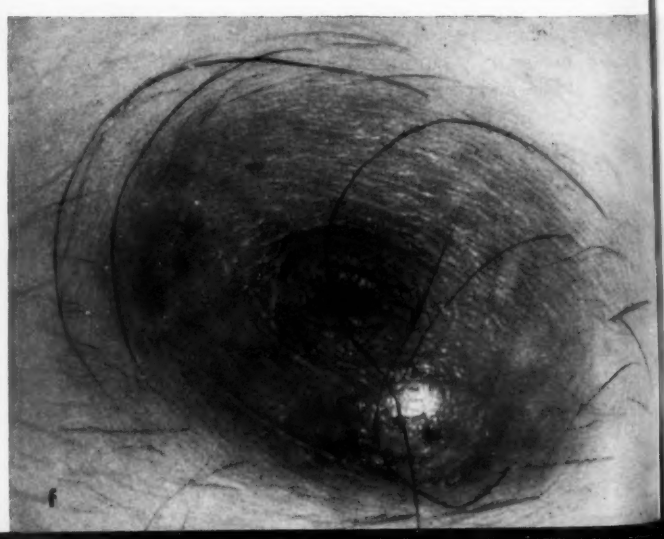


FIGURE 3. Inflammatory lesions.
a. Acute lactation mastitis.
b. Chronic mastitis; mass present five years following pregnancy.
c. Specimen from (b) showing thick-walled abscess.
d. Terminal duct infection; sinus at edge of areola.
e. Terminal duct infection; fixation and retraction of nipple suggesting carcinoma.
f. Nipple and areola with infection of Montgomery's follicle at the lower pole.

have a marked cancerphobia. A good uplift brassiere worn day and night helps. Symptomatic therapy includes ice or heat, anodynes, and restriction of sodium and fluid intake. Estrogens, progesterone and androgens have all been used. Progesterone or testosterone seems more logical and occasionally is helpful. Cystic fluid may be aspirated and if the fluid is clear, regular observation is all that is necessary. If the fluid is bloody or if the cyst repeatedly refills it should be excised. When dominant areas appear they must be excised for biopsy since the differential diagnosis from cancer can be difficult. Simple mastectomy is



done rarely and only for extremely painful disease or grossly abnormal breasts.

Effects of pregnancy and lactation—The response in the breasts to the hormonal changes of pregnancy and lactation is tremendous. During the second month of pregnancy the patient notices sensations of tingling or prickling and a feeling of fullness and tenderness. Soon after, the breasts begin to increase in size. The nipples enlarge and are more erectile and become more deeply pigmented. The areolae become broader and also more deeply pigmented. Montgomery's follicles become more prominent and a secondary areola may appear, especially in brunettes. By the third month a few drops of colostrum can be expressed from the nipples. By the fifth month the peak of development is reached, and any further increase in breast size before delivery is due chiefly to accumulation of colostrum in the acini of the lobules. On the third or fourth postpartum day the breasts suddenly begin to enlarge again; milk is being produced in quantity, and under the stimulus of nursing its production is maintained until the child is weaned.

Abnormalities of lactation—The quantity of milk secreted varies from absolute absence (agalactia) to such excesses (polygalactia) that milk runs from the nipples almost constantly even though the patient wet-nurses a second baby. Happily, the in-between degrees are the more usual. The size of the breasts is no measure of the amount of milk to expect; small breasts are often rich in glands and produce well, while large breasts may be poor in glands and produce meagerly.

Painful engorgement—At the start of lactation, the lymphatic and venous stasis in the breast stroma plus the distention of the acini with accumulating milk produce engorgement which may be very painful. The breasts are tensely distended and acutely tender, the veins beneath the skin stand out, and milk may drip from the nipples, but there is no fever. So-called milk fever means that mastitis is present. When the region of engorgement is limited to a lobule or two we speak of "caked breast." As soon as nursing begins the symptoms are rapidly relieved; in the meantime it helps to support the breasts snugly with a binder, to apply ice bags, and to give small doses of codeine. If at first the baby does not empty the breasts sufficiently, a pump may be used, but if the patient is not going to nurse her baby, the "drying-up" program should be started immediately.

Whenever nursing is to be interrupted or when the mother is not going to nurse her baby at all, it is necessary to "dry up" the breasts. Usually it suffices to bind the breasts tightly against the ribs and to give a mild analgesic for three or four days until the discomfort passes. However, stilbestrol or testosterone, 5 to 10 mg. daily for three to seven days, may be used to speed up the process. The breast should not be pumped or manually expressed even if such action produces some temporary relief; it only prolongs the drying-up period.

Galactorrhea—Occasionally, the nipples will continue to exude a milky secretion for months or years after weaning. This galactorrhea usually stops spontaneously but may continue for 20 to 30 years. The discharge is an inconvenience insofar as it soils the patient's clothing, but no harm comes from it and there is no indication for interference.

Galactocele—Rarely, the blockage of a milk duct by inspissated secretion leads to formation of a retention cyst proximal to the obstruction. The cyst, called a galactocele, may contain milk, or material resembling butter or cheese. The diagnosis can be proved by aspirating the cystic contents. Simple excision suffices for therapy.

Inflammatory Lesions

Nonspecific infections—The nonspecific infections are seen most commonly during or following pregnancy and lactation but are by no means limited to these states and can occur in nulliparae as well as multiparae, at any time from youth to senility, and in males as well as females.

Acute mastitis—This condition is relatively common during lactation, far less common during pregnancy, and relatively rare at other times, although it can occur in the teen-age virgin and in the senile spinster. Its incidence

among obstetric cases is about 2 per cent; over half of these patients are primiparae. Attempts have been made to prevent mastitis by applying antibiotic creams to the nipples of nursing mothers at regular intervals, but the results have not been promising.

Acute mastitis is a rather severe disorder with generalized symptoms and signs. A patient with a fissured nipple or a caked breast, or one with no precursory lesion at all, suddenly has mounting fever, sometimes chills, and considerable toxemia. The involved breast becomes very painful and tender and all the signs of inflammation appear in it (figure 3a).

Once the disease is established, nursing should be stopped and the breasts dried up. Ice packs are applied and the patient is given penicillin or an equivalent antibiotic. If resolution has not begun in 48 hours, suppuration follows and fluctuation appears. The treatment becomes surgical. A radial incision or incisions are made into the abscess and all partitions are broken down with a finger. A drain or gauze pack is placed in the wound and shortened each day. Healing is usually prompt.

A word of caution! If what you think is mastitis persists for two weeks and does not suppurate, get tissue for biopsy; it may be an inflammatory cancer; this is especially true in a pregnant or lactating patient.

Chronic mastitis—Occasionally the course of mastitis is milder and more chronic and characterized by remissions and exacerbations (figure 3b). Suppuration may not occur at all or there may be slow liquefaction with abscess formation (figure 3c). The course may run for many years and as time goes on the differentiation from cancer or a "cancer cyst" may be difficult. The treatment is segmental resection of the area of breast containing the mass, and microscopic analysis.

Terminal duct infection—Also called periductal or plasma-cell mastitis, this form of mastitis differs enough from the ordinary varieties to deserve separate mention. Bacteria gain entrance to the ampullae of the terminal collecting ducts, probably through the nipple, and set up infection. There is a great deal of periductal inflammation, often with a rich infiltrate of plasma cells. At the height of the reaction a large area of the breast may be involved, but the focal point lies at the areola rather than peripherally. Palpation may detect distended ducts which feel like worms. There is little, if any, constitutional reaction. These lesions often suppurate and point through the edge of the areola (figure 3d). This spontaneous drainage is not adequate and a chronic sinus forms, surrounded by an area of induration in the breast around and beneath it. From time to time (the interval may reach several years), there will be a flare-up followed by drainage through the sinus.

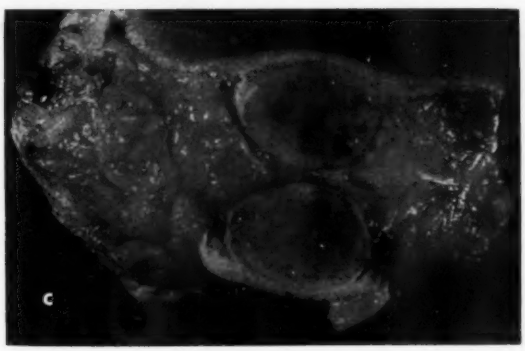
During the acute phase, treatment consists of surgical drainage, hot wet dressings and antibiotics. After subsidence, resection of the involved segment of breast offers the best chance for cure. The induration and retraction of the nipple and areola which occur in this disorder may be difficult to differentiate from cancer (figure 3e).

Infection of Montgomery's follicles—In the areola, spaced circularly about the nipple, are Montgomery's follicles. At any time of life, but especially during pregnancy, an acneform infection may develop in one or more of them (figure 3f). It is treated by opening the abscessed gland with sterile precautions.

Specific infections—Specific breast infections are becoming quite rare. The only one of any importance is tuberculous mastitis which is seen now and then in sanitoriums and in indigent populations. The patient usually has an active focus elsewhere, and the infection is characterized by painless induration and nodularity of the breast, often of long duration, usually with multiple sinus formation and enlargement of the axillary lymph nodes. Biopsy will establish an accurate diagnosis. If the breast alone is involved, simple mastectomy is enough; if the axillary nodes are also involved, a modified radical mastectomy is done, sparing as much of the pectoral muscles as possible. An appropriate chemotherapeutic program is carried on continuously before, during and after the operation.

Sarcoidosis, syphilis and fungous infections of the breast are mentioned by Geschickter as occasional specific infections of the breast.

FIGURE 4. Neoplasms.
a. Lipoma along pectoral ridge.
b. Sebaceous cyst.
c. Specimen from (b) cut open.



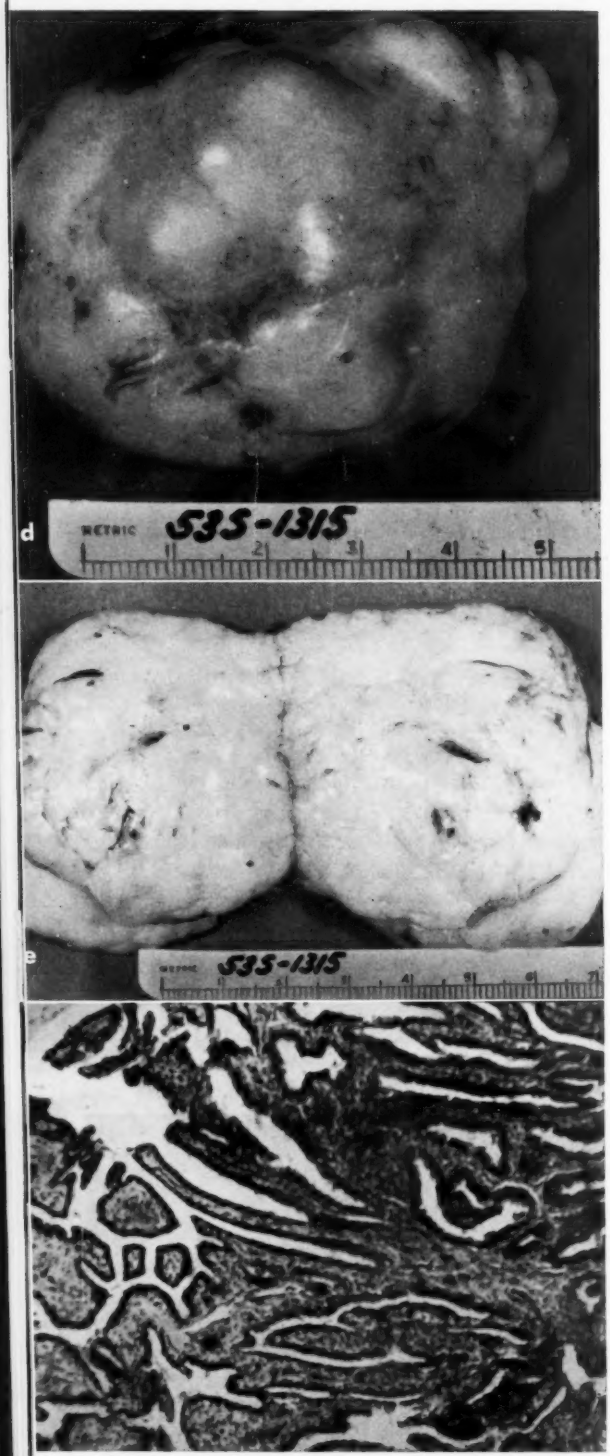


FIGURE 4 *(continued)*

d. Fibroadenoma showing smooth encapsulated surface.
e. Fibroadenoma, cut surface, showing whorls and plugs.
f. Microscopic appearance of intraductal papilloma, showing stalk and friable fronds.

Fat necrosis—This may occur in the breast following infections or trauma. Microscopically, there is an area of necrosis in the breast fat showing xanthomatosis and cholesterol crystals surrounded by granulation, phagocytes (foam cells) and giant cells. Clinically there is a hard fixed area with attachment and retraction of skin. Again, differentiation from cancer is difficult and excisional biopsy establishes the true nature and suffices to cure.

Benign Neoplasms

Benign tumors such as lipomas, xanthomas and sebaceous cysts arise from the stromal or epithelial elements not specific for the breast. These are called nonindigenous tumors. In addition, tissue elements specific for the breast give rise to fibroadenomas from the glandular epithelium and stroma, and intraductal papillomas from ductal epithelium.

Nonindigenous tumors—Lipomas are most often found along the pectoral ridge but can be located anywhere in the breast. They tend to be protuberant and may be visible (figure 4a). They are well encapsulated and quite discrete but are much softer than fibroadenomas. The cut surface is smooth, lobulated and a uniform shiny yellow color.

Xanthomas are rare and may be related to fat necrosis. When involving the skin they have a firm, shiny exterior; the cut surface is a granular yellow, and cells with "foamy" cytoplasm are found microscopically.

Sebaceous cysts arise from the skin of the breast but may protrude inward. In addition to being fixed to the overlying skin, they are quite discrete and have a dark dimple marking the site of the occluded duct (figure 4b). On cut surface they present the characteristic cheesy-grayish or yellowish-white sebum within a thin capsule (figure 4c).

Fibroadenomas—These are the commonest of the benign tumors. They occur in early adult life or even in the early teens, but be-

cause they are symptomless they may go unnoticed until the fifth, sixth or even seventh decade of life. They have a firm, rubbery feel, and are very discrete and mobile. We say they are "poppable" in the breast tissue. They may be smooth or lobulated, solitary or multiple, and affect one or both breasts. The older ones may contain calcium which will cast a roentgenographic shadow. On gross section there is a well-defined capsule, glistening pinkish-white color, and a whorled surface with small protruding plugs (figure 4d and e). On microscopic section the whorls are seen to be thick collars of fibrous tissue compressing sparse glandular elements (the plugs on cut surface) scarcely one or two cell layers thick.

Although the clinical diagnosis can be quite accurate, it is well to excise fibroadenomas locally to be certain of their exact nature and because a small percentage give rise to giant myxomas or sarcomas. The bulky myxomatous tumors, which Johannes Müller called "cystosarcoma phyllodes" because of their microscopic appearance, are usually benign but occasionally contain areas of sarcoma or carcinoma. Whether benign or malignant, they are usually treated by thorough simple mastectomy. When fibroadenomas themselves undergo malignant change they become sarcomas, indicating that the stromal elements play the important role in the neoplasia. In Geschickter's series about 50 per cent of fibrosarcomas seemed to arise from fibroadenomas.

Intraductal papillomas—These papillomas are polypoid projections of ductal epithelium into the lumina of the breast tubules, often with a localized cystic dilatation of the duct so that some authors prefer the term intracystic papilloma. These papillomas are almost always located centrally beneath the areola or close to it and are usually well under 1 cm. in diameter. Microscopically they consist of a stalk from which the neoplastic epithelium protrudes in delicate frondlike prolongations (figure 4f).

Papillomas account for most nipple discharges except those related to lactation. In particular, they account for most instances of bleeding from the nipple. Bleeding from the nipple seems to frighten both the physician and the patient unduly. In only a very small percentage of instances of bleeding from the nipple is a malignant lesion present. In the overwhelming majority of those in which there is a malignant lesion, other important clues will indicate the diagnosis, such as a suggestive mass, a cyst which contains blood on aspiration, or an area of skin attachment. There is always time for a careful work-up of the patient.

When a patient presents herself with bleeding from the nipple, an attempt is made to find a retroareolar nodule or a cordlike, distended duct. If neither is found, pressure is made with one finger at short intervals about the areola in an effort to express blood and thus locate the segment of the breast which contains the bleeding lesion. If the necessary information is not gained at the first examination, the patient is checked at two week intervals until the segment of breast to be excised is determined.

Occasionally, there will be bleeding from several of the duct openings in a nipple or from both nipples, indicating that the process is a diffuse one, so-called papillomatosis. Also, occasionally during a routine physical examination a nodule may be felt in the retroareolar area which, when excised, proves to be an intraductal papilloma although there has been no nipple discharge.

After the duct in which the blood arises has been located, it is exposed surgically and a wedge of breast tissue containing the duct and its tributaries is excised from the nipple well toward the periphery of the breast so that the papilloma will not be left behind. Paraffin sections are usually necessary to determine whether the lesion is benign or malignant. If a report of malignancy is returned the breast should be removed by radical mastectomy.

Summary

Benign diseases of the breast are, in the main, surgical problems. Often the diagnosis involves differentiation from carcinoma, which can best be accomplished by biopsy. Excision of tissue for this purpose usually also suffices for cure of benign lesions. Simple mastectomy should be an infrequent procedure.

Thrombo-embolic Accidents

ORMAND C. JULIAN

Chicago, Illinois

ORMAND C. JULIAN

SOME form of intravascular thrombosis is responsible for acute emergencies of the vascular system other than those which are the direct result of trauma. The thrombus may produce acute arterial or venous occlusion at the site of origin, or it may become detached from its primary focus and become an embolus and produce disturbances elsewhere in the vascular system. Although the manifestations of these conditions are widely diverse and dependent on the region of the arterial or venous system affected, it is useful to consider them as a closely related group of conditions under the term thrombo-embolism.

Thrombi arise in four regions in the cardiovascular system. The initial effect and inherent dangers differ according to the site of origin of the thrombi. (1) Clots in the arterial system occur because of some underlying arterial pathologic process, ordinarily, arteriosclerosis. The local effect is an acute arterial occlusion. (2) Thrombi arise centrally within the heart in response to a recognizable underlying lesion. The predisposing disease is commonly myocardial infarction which stimulates the formation of a mural thrombus on the endocardium overlying the area of the heart muscle involved by the infarction. Atrial fibrillation alone or associated with mitral stenosis stimulates the formation of thrombi within the atrium. Such thrombi within the heart chambers rarely produce any local effect, but when they are dislodged by the contractions of the heart they become emboli which pass out through either the systemic or the pulmonary arteries to produce acute arterial occlusion wherever they lodge. (3) Thrombi commonly develop within the thoracic or abdominal aorta when advanced ulcerating arteriosclerosis is present. These thrombi may be detached before they produce complete occlusion of the aorta, and they provide a not infrequent source of peripheral arterial occlusion in the lower extremities. (4) Thrombosis within the venous system gives rise to acute local changes because of the venous occlusion it produces. The potential danger of such thrombosis is that the clots may become detached and travel through the venous channels to the heart and thence to

the pulmonary arterial system where they produce pulmonary embolism.

The majority of the conditions outlined are acute and should be considered medical and surgical emergencies of high grade. The initial treatment and the early diagnosis determine to a large degree the success of final definitive treatment. I shall outline the early diagnosis of these various thrombo-embolic conditions, their emergency treatment and definitive management.

Acute Venous Thrombosis

Two important elements are present in every case of acute venous thrombosis. One is inflammation of the vein wall and the immediately surrounding tissue; the other is the clot within the lumen of the vessel. In each individual case the comparative importance of these two elements varies widely. The clinical manifestation of inflammation of the wall of the vein and involvement of the surrounding tissue is the appearance of pain and heat, and the development of swelling due to venous and lymphatic obstruction. In cases in which inflammation has been the predominant feature and these signs have been well marked, the term "thrombophlebitis" has been used to describe the condition. On the other hand, in cases in which pain has been minimal, and heat has been absent and the swelling has been discernible only by careful measurement, the condition has been termed phlebothrombosis.

It is not justifiable, however, strictly to divide thrombotic venous disease into these two groups because they are not by any means different entities. In many cases the disease starts as a bland intravenous clot without acute symptoms, and may progress and produce all the signs of inflammation associated with thrombophlebitis. These conditions are seen almost exclusively in the lower extremities. The cause varies widely, and these conditions may occur secondary to almost any lesion, disease or surgical procedure anywhere in the body. In many instances, a clear, precipitating condition cannot be demonstrated.

Diagnosis—The recognition of acute thrombophlebitis in the presence of the usual amount of inflammation is rarely difficult. Pain, heat and swelling occur early. A general febrile reaction is present, and venous obstruction is evidenced by the presence of increased tension in the subcutaneous veins in the distal part of the extremity, and dilatation of the veins is visible through the skin over the entire involved area. It is particularly on the basis of the very diffuse nature of the inflammatory signs and on this venous distention that thrombophlebitis of the acute type is distinguished from tissue inflammation or from cellulitis.

The bland form of venous thrombosis is an important diagnostic problem because of the frequency with which emboli become dislodged from a vein in the lower extremity and produce pulmonary embolism. The early diagnosis of bland intravenous thrombosis after operation or in cases in which medical treatment is being used has been widely emphasized. Its early discovery in such cases will depend on frequent examination for venous distention in the lower extremities or for the onset of tenderness in the calf. Owing to the frequent appearance of papers on this subject, an attempt to elicit a Homans' sign has become one of the most useful diagnostic procedures after operation.

The course to pursue when the presence of phlebothrombosis is suspected or when it is known that this condition is present is not nearly so well understood as is the diagnosis. On the basis of reported clinical experience with methods of treatment of phlebothrombosis aimed at prevention of pulmonary embolism, one must at present conclude that properly applied anticoagulant therapy with heparin and DICUMAROL® is the treatment of choice. In applying anticoagulant therapy, the purpose should be to control the coagulation time as desired and to keep the complications resulting from the therapy itself at a minimum. This can best be done by the use of a simple and routine method of administration, the control of which does not exceed the scope of the laboratory facilities which are used to follow the effect of the drugs. Heparin is used initially because of its immediate effect, and its administration is controlled by the determination of the coagulation time of

the patient's blood. The aim should be the prolongation of the clotting time to three times the routine normal as determined by the laboratory. It is true that refinement of the technic of determining the coagulation time progressively results in longer and longer normal readings. Careful handling of blood specimens and attention to the cleanliness of the tubes used for the test largely determine what the normal shall be for any individual laboratory. This normal, however, may remain quite constant and is a sufficiently reliable guide for heparinization.

Before any therapy is started, the patient's prothrombin and coagulation times are determined in order to prove that the patient does not have any condition resulting in hypoprothrombinemia. This would entirely upset anticoagulant therapy and incidentally would be cause for reconsideration as to the true meaning of the thrombophlebitis which is being treated. The initial prothrombin time is determined before heparin administration is started. If the prothrombin time and the coagulation time are normal, 100 mg. of crystalline heparin is administered intravenously at the ordinary rate. At the same time, an order may be left to administer heparin in the same form by a subcutaneous injection subsequent to the initial intravenous dose. The dose and the interval between injections can be varied from 50 mg. every three hours to 30 mg. every four hours, depending on the effect on the coagulation time.

The coagulation time should be determined as early as possible every morning when the laboratory opens and as late as possible in the afternoon or evening before the routine laboratory technicians go off duty. If the routine normal coagulation time in a laboratory is approximately eight minutes as determined by the test tube method, the desired time should be 18 minutes. A capillary tube method of determining the coagulation time should never be used; instead, the Lee-White test tube method or some modification of it must be used. This method of administering heparin has the advantage that it can be carried out by the nursing staff and the disadvantage that it requires multiple insertion of needles for the administration and control. It is far more economical than any method of carrying on heparinization by the intravenous route and only slightly more expensive than the use of heparin in an absorption-retarding menstruum. The subcutaneous injection is rarely painful and is usually tolerated by the patient for the required two or three days until the Dicumarol therapy, which is started simultaneously, has become effective.

If the initial prothrombin time is normal and the patient has no evidence of liver or renal disease, Dicumarol therapy can be started in a routine fashion. The oral administration of 100 mg. of Dicumarol every eight hours until six doses have been given ordinarily will result in a satisfactory depression of the prothrombin activity on the third day of therapy. The aim of administration of Dicumarol should be the reduction of the prothrombin activity of the patient to a range of 30 to 40 per cent of normal. The effect of the drug must be followed by daily determination of the prothrombin time, at least in the early stages of treatment, until the response to be expected of the individual patient is learned. Even if the therapy is to be prolonged, it is an assumption of risk if this determination is not made at least twice weekly. Dicumarol therapy cannot be offered a patient unless the prothrombin time can be determined.

Ligation of the involved vein proximal to the clot is available as an additional or alternative method of treatment in preventing pulmonary embolism in cases of diagnosed phlebothrombosis. It is much less widely used now than it was two or three years ago, because of the equal ability of anticoagulant treatment to prevent embolism. Vein interruption may be considered to be indicated in the following types of patients: (1) Patients who have a demonstrable degree of liver disease. Such patients are to be suspected of having some suppression of the plasma prothrombin and may be unsafe subjects for anticoagulant therapy. (2) Patients with renal disease. (3) Pregnant women in whom the administration of anticoagulants has been shown to affect the fetal coagulation system far more than it does that of the mother. (4) Patients who recently have

had surgical procedures on the central nervous system or on the urinary bladder, or operations which required extensive dissection of tissues. In such patients enzymatic absorption of an already formed clot is normally buttressed by the formation of new clots. This mechanism for the maintenance of hemostasis would be destroyed by the anticoagulant treatment. (5) Patients with distinct bleeding tendencies or those having a blood dyscrasia or purpura. (6) Patients who are being treated where there are inadequate laboratory facilities to provide safe control of the anticoagulant therapy. (7) Patients who have had more than one attack of pulmonary infarction and in whom anticoagulant therapy has been instituted after the first attack, or patients in whom pulmonary infarction occurs in spite of adequate anticoagulant treatment.

The use of anticoagulants is not necessarily directed only toward the prevention of pulmonary embolism, but is considered to have some significant effect on the local problem in the extremity. Extension of the intraluminal thrombus with progressively greater obstruction of the vein is diminished. Precipitation of fibrin in the intercellular edema fluid is also minimized, and the absorbability of this fluid is maintained.

Of equal importance in preventing pulmonary complications of thrombophlebitis is the management of the local condition. Future prolonged periods of disability due to recurrent attacks of thrombophlebitis and chronic stasis disease resulting from damage to the veins can be prevented or reduced in severity by proper management during the acute period. The dominant part of this management consists of a rational program of ambulation. Initially, the patient is kept in bed with the involved extremity or extremities elevated until all of the edema has disappeared. During this time, the patient is encouraged to move his legs, but anything more than moderate exercise is avoided. When the edema has subsided, graded and gradually increasing periods of ambulation are allowed within the limits of the formation of any swelling. At the beginning of this period of ambulation, the patient may be allowed up for 10 minutes of each hour and is encouraged to walk about rather than to sit or stand still. After one or two days at this stage, if no edema has resulted, the time that the patient is permitted to be up is increased, but should not be long enough to cause edema.

This program will be tolerated by the patient only if the purpose of preventing future trouble is carefully explained. The time lost during this period will be amply repaid in the freedom from the late effects of chronic stasis disease. The use of elastic supports in the form of well-made elastic stockings is begun when the period of ambulation has reached a length sufficient to justify their use. Elastic bandages on the legs are distinctly not indicated during the period of rest in bed, and insofar as is practical they should be removed during all periods of rest during the day in cases in which ambulation is progressing. Only in rare instances need the stocking be longer than knee length. Its weight should be heavy, and the heel should be enclosed with the elastic material. Maximal wear and comfort with good support have been obtained with stockings that are designated as one-way stretch in that they are heavier and have less tendency to slip down on the leg.

Acute Arterial Occlusion

Diagnosis—The important signs and symptoms of acute arterial occlusion in an extremity are in the main independent of the pathologic process causing the obstruction. Acute occlusion, except when caused by trauma, is due to a thrombus within the arterial lumen. As was mentioned in the opening paragraph, this thrombus may form *in situ* in response to a disease process of the artery or may lodge there after having arisen as an embolus within the chambers of the heart or on an ulcerated plaque within the aorta.

The complaints of the patient consist of pain, coldness, numbness and paralysis. Sudden pain is usually the initial symptom, but its degree varies widely, and in a significant number of cases the pain may be quite mild or absent. Coldness, numbness and paralysis occur in almost all cases.

The signs found on physical examination

consist of coldness of the skin to touch, pallor and cyanosis, paralysis of the muscles in the distal part of the extremity, anesthesia, loss of palpable pulse, lack of venous filling, and absence of pulsation as shown by the oscillometer. Tenderness usually is not a prominent feature.

This combination of signs and symptoms occasionally may be reproduced in the absence of a true arterial obstruction, and certain points in differentiating them are important. Vasospasm may be of sufficient degree to bring on pallor and cyanosis, the loss of palpable pulse, coldness, and even relative weakness of the muscles in the foot or hand of the involved extremity. Severe pain is a regular accompaniment of this degree of arterial spasm. The acute onset of thrombophlebitis in persons who are vasosensitive, crushing trauma not necessarily severe, and herniated intervertebral disks are some of the conditions which may produce a severe degree of vasospasm. A most important factor in the differential diagnosis is the absence of cutaneous anesthesia in all of these conditions. The hypesthesia accompanying a slipped disk should readily be distinguished from that of an acute arterial occlusion.

Treatment—The most important consideration in the treatment of acute arterial occlusion is that the condition comprises a surgical emergency and that all treatment should be instituted as early as possible. Early diagnosis is, therefore, of unusual importance and is almost never difficult. However, even if the proper diagnosis is made, a full realization of the emergency nature of the condition has often been lacking. Many patients have been deprived of the fine functional result which usually may be obtained by proper therapy. Some of the fault is due to numerous reports of conservative management which would seem to indicate that recovery will occur in many cases if nothing more than a few supportive measures are applied. This point of view, which may very well have been valid before the development of present day arterial surgery, is certainly unacceptable at present.

After the diagnosis of an acute arterial occlusion has been made, therapy may be divided into immediate treatment, definitive treatment, and late treatment. In the immediate treatment, it is not important to determine either the cause of the acute obstruction or its level. Measures are used to increase the efficiency of the collateral circulation by relief of reflex arterial spasm and to prevent an increase in the extent of the obstruction by propagation of the clot. Reflex vasospasm in an extremity is most effectively relieved by the injection of procaine hydrochloride about the sympathetic ganglia supplying the region. This involves doing a stellate ganglion block in cases of acute occlusion occurring in the arm, and lumbar sympathetic block in cases of involvement of the lower extremity. The intravenous administration of heparin diminishes the propagation of the thrombus from the point of occlusion.

Unfortunately, these two procedures may not be safely used simultaneously because of the danger that the anticoagulant will lead to serious hemorrhage at the level of introduction of the needle for the ganglion block. In order to obtain both effects, it is evident that the sympathetic block should precede the administration of heparin by some 15 to 20 minutes. This is not always feasible because patients with this acute condition are often seen in their homes where it is impractical to be prepared for a procaine block of the sympathetic chain. On the other hand, it is quite easy to order and administer heparin before hospitalizing the patient. A small dose of heparin, perhaps 50 to 100 mg., may be administered intravenously at home, and it will be found that when the patient arrives in the hospital an hour later the coagulation time is no longer dangerously prolonged.

In cases of involvement of a lower extremity, another method of obtaining temporary sympathetic paralysis is available, namely, an epidural block with procaine hydrochloride through a caudal needle. By this approach, and with very little specialized equipment, a polyethylene tube of tiny caliber may be introduced through the needle within the caudal canal and left *in situ* so that additional procaine hydrochloride may be injected from time to time without the hazard of having to

insert a needle again. This method of administration seems to be quite compatible with continuing heparin therapy.

Other methods than the introduction of procaine hydrochloride around the sympathetic chain or into the epidural space are available for the relief of vasospasm. Reflex vasodilatation is obtained by applying heat to the central parts of the body. The use of drugs is in the main unsatisfactory, but the oral or subcutaneous administration of relatively large doses of papaverine hydrochloride is effective to some degree. Two grains of the drug given subcutaneously is the usual dose.

The application of all of these methods of diminishing spasm and growth of a blood clot is useful and desirable. The general physical state of the patient, however, must be considered so that too much treatment is not applied. This treatment, when combined with a rapid trip to the hospital, could result in an exhausted and dangerously ill patient if his initial condition was critical. Immediate embolectomy or thrombectomy, done under local anesthesia, may be the safest treatment.

There is little disagreement that *definitive treatment* of an acute arterial occlusion consists of the early surgical removal of the obstruction. It is seldom that a patient cannot be brought into a satisfactory state for the removal, under local anesthesia, of an embolus in an artery within a limb. When a more severe obstruction is present, such as an embolus lodged at the aortic bifurcation, the patient's ability to withstand a major operation under general anesthesia may be considered to become less important. This contradiction arises from the fact that removal of an acute obstruction at the aortic bifurcation is lifesaving and must almost routinely be attempted. When the obstructive lesion is an embolus, early removal may be expected to be successful in a large percentage of cases. Removal of a thrombus from the lumen of an arteriosclerotic vessel, however, is a far more difficult problem, and success will not be obtained in a high percentage of cases by the most experienced surgeon.

Immediately after surgical removal of such an obstruction, the patient should be mobilized as much as possible in bed, and early ambulation should be insisted on within the limits of the patient's general physical state. The anticoagulant therapy is continued during the recovery period to help prevent the formation of a thrombus at the site of the thrombectomy. Anticoagulants have also been demonstrated to be useful in preventing further emboli from the source in a fibrillating heart or a heart in which there has been a recent myocardial infarction.

MEETINGS *and Postgraduate Courses*

AMERICAN COLLEGE OF CHEST PHYSICIANS: Eighth annual postgraduate course on diseases of the chest at the Bellevue-Stratford Hotel, Philadelphia, March 7-11. Further information may be obtained from the Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

UNIVERSITY OF MINNESOTA, MINNEAPOLIS: Continuation course in clinical hematology for physicians at the Center for Continuation Study, February 28-March 2.

UNIVERSITY OF MINNESOTA, MINNEAPOLIS: Continuation course in emergency surgery for general physicians, March 31-April 2, at the Center for Continuation Study, under the direction of Dr. Owen H. Wangensteen, Professor and Chairman, Department of Surgery.

Continuation course in cardiovascular diseases for general physicians, sponsored jointly by the Minnesota Heart Association, March 21-23, at the Center for Continuation Study. Program is directed by Dr. C. J. Watson, Professor and Head, Department of Medicine.

Scientific Exhibit

Combined Ocular and Cutaneous Manifestations of Disease

MANUEL FRANCISCO ALLENDE AND PHILLIPS THYGESON*

University of California School of Medicine, San Francisco

MANY diseases affect both the eyes and the skin. These may be localized diseases chiefly of interest to the ophthalmologist or the dermatologist, or the cutaneous and ocular changes may be a manifestation of systemic disease. It is in the latter that familiarity with these visible lesions can be of great diagnostic value.

This exhibit illustrates a few examples of associated cutaneous and ocular manifestations of disease selected on the basis of frequency, vital importance or diagnostic value.

*Departments of Dermatology and Ophthalmology, University of California School of Medicine, and the Francis I. Proctor Foundation for Research in Ophthalmology, San Francisco, California.

Adapted from an exhibit at the Annual Meeting of the American Medical Association at San Francisco, June 1954.

FIGURE 1. Staphylococcic blepharitis.

FIGURE 2. Diplobacillary blepharitis.

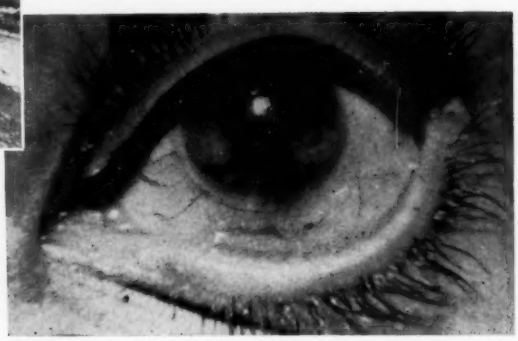
Superficial Bacterial Infections

Superficial bacterial infections of the eye can affect the lids, producing blepharitis. Staphylococcic blepharitis is characterized by dry, brittle scales on an erythematous base, in contrast to the greasy, yellowish scales of seborrheic blepharitis which is usually seen in conjunction with seborrheic dermatitis of the scalp.

Diplobacillary blepharitis is angular in localization and is often accompanied by excoriations at the anterior nares.

FIGURE 3. Sarcoidosis. Nodules on skin.

FIGURE 4. Sarcoidosis. Uveitis.



Sarcoidosis

In most cases of sarcoidosis there is both ocular and cutaneous involvement in addition to other systemic lesions. Skin lesions consist of deep nodules, papules or superficial plaques. Typical ocular lesions include granulomatous uveitis and interstitial keratitis. These visible lesions are of great value in diagnosing sarcoidosis.

Syphilis

Ocular and cutaneous lesions are very important in the diagnosis of syphilis.

In primary and secondary syphilis, dark field-positive chancre and maculopapulopustular lesions are present. Iridocyclitis may be seen.

In late syphilis, gummas are still occasionally seen. Ocular lesions consist of ophthalmoplegia, ptosis, Argyll Robertson pupils, and optic atrophy.

In congenital syphilis, cutaneous lesions which may be bullous appear at birth or shortly after. Interstitial keratitis is a manifestation of late congenital syphilis.

FIGURE 5. Interstitial keratitis, syphilitic.

FIGURE 6. Herpes simplex. Dendritic keratitis, late. ▶

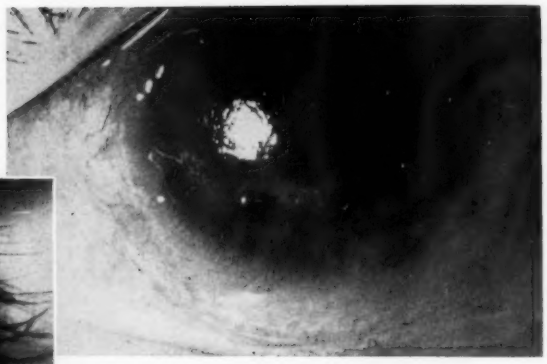


FIGURE 7. Herpes simplex. Dendritic keratitis, recurrent.

Herpes Simplex

Herpetic infections of the skin are usually benign, causing discomfort only when recurrent. An exception is eczema herpeticum (Kaposi's varicelliform disease), a fulminating graft of herpes simplex virus on the skin of a child with atopic dermatitis.

Ocular lesions are very serious, since important visual loss can result from corneal scars produced by typically recurrent dendritic keratitis.

Herpes Zoster

Herpes zoster usually causes transient discomfort. In an occasional case, severe postherpetic pain becomes intractable.

When the nasociliary branch of the ophthalmic nerve is involved, severe keratitis with uveitis and occasionally secondary glaucoma can occur.

Generalized herpes zoster can be associated with leukemia.

FIGURE 8. Ophthalmic herpes zoster.

Vaccinia

FIGURE 9. Accidental vaccinia.

Generalized vaccinia is rare. Occasionally, accidental transfer to the eyelids, conjunctiva and cornea occurs. In rare instances, postvaccinal encephalitis with retinitis, optic neuritis and ocular muscle paralysis has been noted.

In cases of children with atopic dermatitis, the virus of vaccinia can also produce an eczema vaccinatum quite similar to that produced by herpes simplex (eczema herpeticum).

Molluscum Contagiosum

FIGURE 10. Molluscum contagiosum of the lid with follicular conjunctivitis.

The small viral tumors of molluscum contagiosum, when they occur on the lid, produce typical secondary follicular conjunctivitis which may simulate trachoma.

Contact Dermatitis

FIGURE 11. Contact dermatitis of the lid.

Contact dermatitis of the lid is extremely common, due to the thinness of palpebral skin. It can occur even when the offending agent does not affect the immediately adjacent skin, as in cases of nail-polish sensitivity. Nail polish and scalp cosmetics are the most frequent causes. Secondary conjunctivitis can occur.

FIGURE 12. Cataract. Atopic dermatitis.

FIGURE 13. Keratitis. Atopic dermatitis.

Atopic Dermatitis

Skin lesions of atopic dermatitis consist of erythema, scaling and lichenification, chiefly of the face and flexural areas.

The classic complication of early atopic cataract is seen in a large proportion of cases of adults with long-standing atopic dermatitis. A rarer complication, also seen in adults, is severe vascularizing keratitis.

Erythema Multiforme

Severe erythema multiforme of the bullous type generally involves the mucous membranes. The disease has been called Stevens-Johnson syndrome and erythema exudativum pluriorificialis. It probably represents a manifestation of hypersensitivity to allergens, bacterial toxins or viruses, or a combination of these. Eye lesions consist of conjunctivitis which can be catarrhal, purulent or membranous. It may be followed by keratoconjunctivitis sicca due to obliteration of the secretory ducts of the lacrimal glands by scar tissue.

◀ FIGURE 14. Erythema multiforme.

Systemic Lupus Erythematosus . . .

FIGURE 15. Skin lesions of systemic lupus erythematosus.

Skin lesions of systemic lupus erythematosus usually involve the face and extremities and are characterized by erythema and edema. Atrophy and plugging are present only in lesions of long standing.

Fluffy exudates are present in the fundus.

Both the skin lesions and the fundal exudate are of great value in diagnosing the disease.

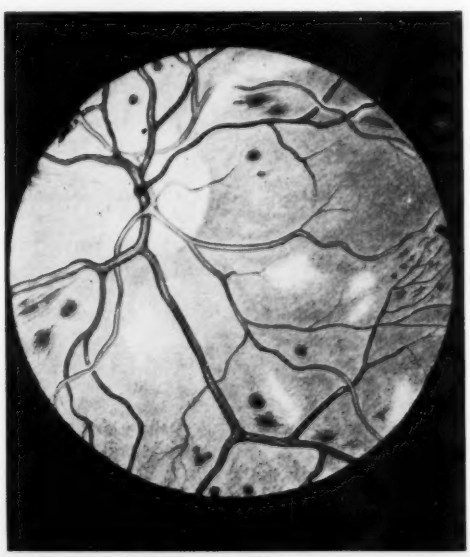


FIGURE 16. Fundal exudates in systemic lupus erythematosus. ▶

Xanthomatosis

FIGURE 17. Xanthelasma.

The most common xanthomatous deposits occur on the lids in the form of the superficial yellowish plaques of xanthelasma. They are seen at times with xanthoma tendinosum and more rarely with xanthoma tuberosum, the latter being more commonly associated with coronary disease. Lipoidal dystrophy of the cornea occasionally occurs simultaneously.

FIGURE 18. Malignant exophthalmos.

Circumscribed Myxedema

Following thyroidectomy, yellowish, pigskinlike plaques may appear on the shins. They are often accompanied by malignant exophthalmos which may have preceded the operation.

Vogt-Koyanagi Syndrome

FIGURE 19. Poliosis eccentrica in Vogt-Koyanagi syndrome.

This rare syndrome comprises uveitis, alopecia, plaques of vitiligo, poliosis eccentrica (patches of white hairs or lashes) and dysacousia. The related uveitis of Harada's disease has the distinguishing feature of bilateral serous retinal detachment with frequent spontaneous reattachment.

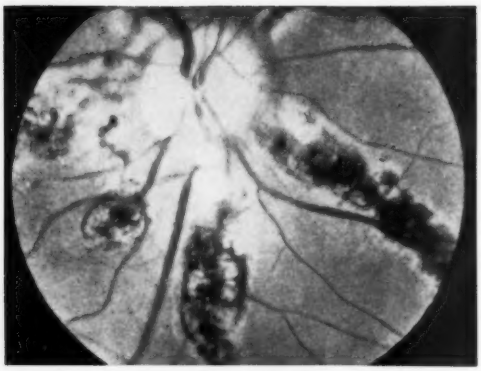


FIGURE 20. Angioid streaks in pseudoxanthoma elasticum.

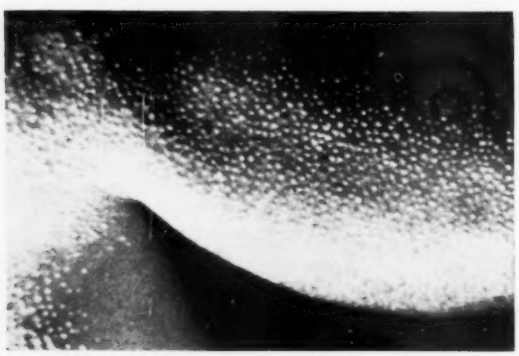
Pseudoxanthoma Elasticum

Widespread systemic derangement of elastic fibers produces typical cutaneous and ocular lesions. Cutaneously, there are symmetric streaks of yellowish papules on the neck and in the axillae and inguinal folds. Angioid streaks of the retina are seen in association with hemorrhage and exudates.

Von Recklinghausen's Disease

The phacomatoses are a group of congenital diseases with involvement of the central nervous system, skin and eye. They comprise epiloia (with tuberous sclerosis of the brain, adenoma sebaceum of the skin and mulberrylike tumors of the retina and disk), Sturge-Weber syndrome (angiomas of the skin and central nervous system and cysts of the retina), and neurofibromatosis (von Recklinghausen's disease), with formation of tumors in all three systems. Bone involvement occurs in 70 per cent of the cases of neurofibromatosis, with pulsating exophthalmos if the roof of the orbit is involved.

FIGURE 21. Neurofibromatosis of the skin.



Vitamin A Deficiency . . .

(Continued next page)

FIGURE 22. Skin lesions of vitamin A deficiency.

Vitamin A Deficiency

(Continued)

In vitamin A deficiency, typical cutaneous lesions consist of follicular hyperkeratosis predominantly on the exterior surfaces. Xerophthalmia and hemeralopia are seen. Bitot's spots of keratinized epithelium starting at the temporal limbus are early signs.

FIGURE 23. Bitot's spots in vitamin A deficiency.

Seborrheic Dermatitis

One of the more common dermatoses (seborrheic dermatitis) involves the scalp, eyebrows, retroauricular spaces and sternal area. The lesions consist of erythema and scaling. Seborrheic blepharitis with its greasy, yellowish crust is almost always present. Rarely, epithelial keratitis occurs.

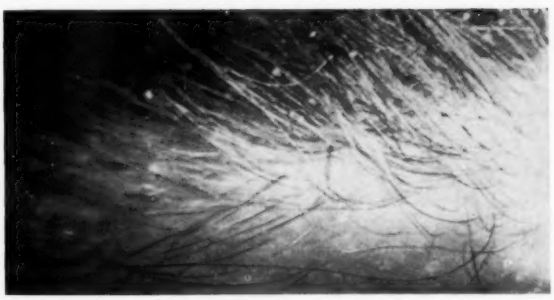


FIGURE 24. Seborrheic dermatitis.

FIGURE 25. Keratitis in acne rosacea.

Rosacea

Rosacea consists of telangiectasia, papules and pustules of the face occurring in middle-aged individuals. It is accompanied frequently by bacterial blepharitis and conjunctivitis and more rarely by severe vascularizing keratitis which usually begins in the lower half of the cornea in the form of a sectorlike pannus.

Pemphigus Vulgaris

Pemphigus vulgaris is manifested by bullae on the skin and mucous membranes of the mouth and eye. It is to be differentiated from ocular pemphigus which produces progressive shrinkage of the conjunctiva and does not involve the skin.

FIGURE 26. Ocular lesion in pemphigus vulgaris.

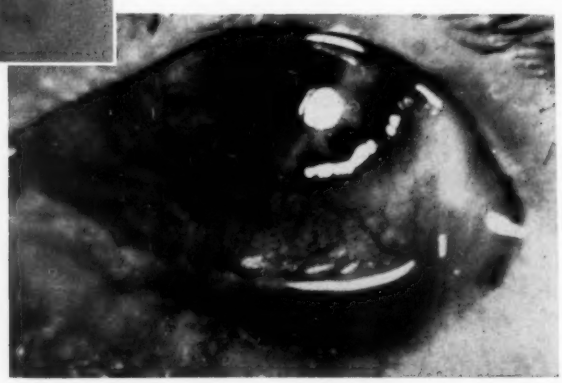


FIGURE 27. Ocular pemphigus.

POSTGRADUATE CONTINUATION COURSE
Southwestern Medical School

Pleural Effusion

H. FRANK CARMAN*

Southwestern Medical School of the University of Texas, Dallas

PLEURAL effusion or hydrothorax means accumulation of fluid in the pleural space. The accumulation may be small, massive, loculated or interlobar. One should avoid the term "idiopathic" because that means that the etiology has not been determined. Pleural effusion is produced by interruption of the normal circulation of the body fluids.

Except in cases in which the effusion is small, diagnosis is fairly simple. There may be few or no symptoms, or the onset may be acute with lancinating pain in the base of the affected side, and a febrile course. With fluid accumulation, the symptoms may abate.

Physical examination may disclose limited motion to the affected side. Tactile fremitus may be diminished or completely absent. There will be dullness to flatness on percussion. The breath sounds will usually be absent. Fluoroscopic examination will usually show increased density in the lower portion of the affected side. The diaphragm may be partly or completely invisible. Usually there will be a fixation or limited motion if the diaphragm can be seen. The x-ray will show a homogeneous shadowing extending up the lateral chest wall with or without visibility of the diaphragm. All these findings will be in proportion to the amount of fluid accumulated in the pleural space.

There are two reasons for removing pleural fluid. First, with the increasing quantity the patient may be uncomfortable and the fluid should be removed to give him relief. Second, it should be done for examination of the fluid. It should be kept in mind always that the effusion itself is not a disease but only a symptom, and it is most important that a diagnosis be made.

Pleural fluids are usually classified as either exudate or transudate. A specific gravity test should be done immediately after removing pleural fluid. Exudates have a specific gravity of from 1.015 to 1.018 and up, while that of transudates is 1.018 or 1.015 or lower.

Pleural fluids are caused by: (1) inflam-

*Clinical Associate Professor of Medicine, Southwestern Medical School of the University of Texas, Dallas, Texas.

Presented at the Ivan H. Mattson I Memorial Tuberculosis Seminar, Dallas, Texas, May 1954.

mation, (2) neoplasm, (3) cardiac decompensation or (4) nephropathy. An exudate usually means that the cause is due to inflammation. Neoplasm may cause an exudate or transudate, usually the latter. Cardiac and renal decompensation will usually produce a transudate.

In addition to determining the specific gravity of the fluid, one should also examine it microscopically for bacteria, by culture and even by animal inoculation. The exudate may be fibrinous or serofibrinous, clear or amber-colored, yellowish or opalescent. With increased infection the fluid may be purulent and thus indicate an empyema. There will be increased proteins and, governed by the amount of infection, there will be leukocytes and lymphocytes with or without red blood cells. It has been said that about 80 per cent of this type of inflammatory exudate is due to tuberculosis. It is not at all unusual to find a patient with rather extensive pleural effusion due to tuberculosis with completely negative x-ray findings of the lung parenchyma.

Even though tuberculosis cannot be demonstrated, it is wise to keep the patient under observation for a period of several months, with limited activity, to determine if tuberculosis will develop. This is particularly important for patients in the younger age group. We have all had the sad experience of seeing a patient with pleural effusion have a thoracentesis and return to work within two or three weeks only to see the same patient 9 to 12 months later with acute fulminating tuberculosis.

In the case of a neoplasm the accumulation of pleural fluid is usually less acute, and the aspirated fluid may contain gross blood and its specific gravity may be in either the transudate or exudate class. Again, the fluid should be examined very carefully, both as to bacterial content and microscopic findings. Examination by Papanicolaou stain should be done to determine if there are tumor cells in the pleural fluid.

Patients with pleural fluid due to cardiac or renal failure nearly always show clinical findings referable to either the heart or kidneys, and the diagnosis is usually fairly simple. In cases of cardiac decompensation the fluid usually begins to accumulate in the right side, and there are generally sufficient parenchymal findings in the lung to make one suspect the diagnosis. In either cardiac or renal failure the fluid may be bilateral.

Pleural aspiration may be needed only once or it may have to be repeated. It is not unusual for fluid to continue to accumulate and it should be aspirated until the pleural space is obliterated. To re-emphasize, examinations of pleural fluid should be done continuously until the etiology is determined. In an occasional case, no satisfactory diagnosis will be made. This is true of a patient now under observation. She has had bilateral effusion with repeated aspirations and repeated studies of the fluid. To date, no absolute proof of its etiology has been made. Both cardiac and renal functions are normal. Repeated examinations for tumor cells have been negative. I feel that it represents an inflammatory exudate, but there have not been enough findings to feel absolutely secure in this diagnosis.

POSTGRADUATE CONTINUATION COURSE
University of Colorado

Diagnosis and Treatment of Acne

JAMES A. PHILPOTT, JR.*
University of Colorado School of Medicine, Denver

ACNE is such a common problem that it is almost physiologic. Almost everyone has a certain degree of acne at some period in his or her life. The most common age at which acne occurs is at the onset of puberty, but it may persist or not even appear until the late teens or twenties or even thirties.

Diagnosis

The clinical picture of acne requires no detailed description. Acne most generally occurs on the face, the upper shoulders and back, and the anterior aspect of the chest. For purposes of classification, acne may be divided into three clinical types: (1) papular, (2) pustular and (3) cystic. It is unusual, however, to see a patient with a pure type of acne. In general the characteristic lesion consists of comedones with papules of an inflammatory nature, and pustules which, as the lesions deepen, become cystic.

Pathology and Physiology

Acne is commonly associated with varying degrees of seborrhea, involving the scalp, forehead, chest and interscapular area. At times the more disseminated type involves the axillae, pubic area and perineal area. Acne may also be associated with a disturbance of apocrine gland function, especially in the axillae or in the pubic area. This condition, in which the apocrine glands are simultaneously affected, is termed hidradenitis suppurativa.

Basically, acne is a disturbance in the function of the pilosebaceous apparatus. There is an alteration in the physical characteristics of the sebum, with a tendency toward hyperkeratosis of the follicular orifices and a deposition of sebaceous material to form a comedo. Following this plugging of the follicular orifices, there is a stasis within the sebaceous glands. Secondary infection commonly follows this static process, helping to produce the inflammatory reaction and the pustule. If the gland becomes dilated enough, cysts form. If the cysts rupture or if invasion occurs, large areas of the skin are undermined by multiple sinuses extending from the sebaceous gland. With the appearance of the sebaceous material in the tissues surrounding the sebaceous gland, there is likely to be a foreign-body type of inflammatory response.

Several factors may affect the alteration in function described.

*Clinical Instructor, Division of Dermatology, University of Colorado School of Medicine, Denver, Colorado.

Presented at the Postgraduate Course in Common Skin Conditions for General Practitioners, University of Colorado, Denver, July 1954.

Hormonal imbalance—It is felt that acne represents primarily a type of hormonal disturbance with a tendency toward increase in androgenic function. This does not mean that there is an absolute increase in circulating androgens. It means, as far as we can ascertain from the experimental work that has been done, that there is an alteration in the ratio of the circulating androgens to the circulating estrogens, with a tendency toward increase in androgenic function. This has been borne out by several different types of clinical experimentation. The altered estrogen-androgen ratio is more marked at puberty and does not stabilize itself for a varying period of time in each person's life. This perhaps accounts for the fact that some individuals may have acneform eruptions late into their teens, while others have little or no acne at puberty. Why one individual has a marked response to this type of imbalance has not been adequately explained.

Diet—Of the many other things that affect the course of acne and aggravate it, diet is one of the more important. Dietary factors do not cause acne, but they tend to aggravate it. The dietary elements ordinarily stressed are foods which are rich in fat content. This subject is covered more thoroughly under the discussion on treatment.

Metabolic disturbances—Disturbances of metabolism also may play a role in acne. The aspects particularly related to thyroid function have been greatly stressed by some workers, who feel that no acne regimen is complete without a small amount of thyroid extract, whether or not there is any abnormality in the patient's basal metabolic rate and whether or not hypothyroidism is suggested. I personally have not included thyroid extract in all instances, although I think that occasionally it is beneficial.

Climatic conditions—People who live in hot, humid areas are much more likely to have aggravation of their acne during the hot seasons of the year, especially those who have cystic acne. Many servicemen sent to the South Pacific had to be evacuated because of this. If evacuated by boat, many of them were almost cured by the time they returned to this country. If they flew back they still had their acne when they arrived, but in many cases it cleared up with little or no treatment except cleansing with soap and water and an astringent lotion.

Emotional stress—Emotional stress certainly seems to be important on an empiric basis. For example, in college students acne is notoriously worse during the final examination period. Whether the cause is emotional stress or lack of sleep or a lot of snacks consisting of hamburgers and soft drinks instead of three meals a day is hard to say. Some patients state quite frankly and emphatically that their acne flares up whenever they are in a state of emotional stress or fatigue, so one cannot entirely discount this aspect of the aggravation of the condition.

Medications—Certain medications aggravate acne, particularly drugs which contain halogen derivatives—iodides, bromides. This is more of a problem in older persons who still have acne. Also well known is the effect of steroids, ACTH and cortisone on the development of acneform types of eruptions. Certain hydrocarbons which come in contact with the surface of the skin, particularly chlorinated hydrocarbons, may produce an acneform eruption or aggravate a pre-existing one. This is particularly true in electrical workers, people who handle electric wiring. The protective waxy covering of many types of electric wiring contains a chlorinated hydrocarbon which aggravates acne and produces an occupational type of acneform disturbance.

Focal infection—The role of focal infection in aggravating acne should be mentioned. Here again some authorities emphasize focal infection more than others. However, in certain instances acne improves after removal of a focal infection of the tonsils or the teeth.

Treatment

The over-all treatment of acne can be routinized in many respects but certainly must be individualized, depending somewhat on the type of acne present.

Diet—In general, when a patient comes in for an evaluation of his acne for the first time, he receives an outline of a diet which is low

in fat and fat-containing foods. Chocolate heads the list of foods which aggravate acne. Cola drinks are another common offender. Foods rich in iodine content—such foods as cheese, and particularly processed cheese, which contains a fairly high content of iodine —are important. Ice cream is another. In some individuals iodized salt may be enough to tip the balance, so to speak. We try to restrict foods which are particularly stimulating and which contain large amounts of seasoning, such as chili sauce, catchup, mustard, and the like. Seafood may be a problem.

We try to limit consumption of pork and fatty meats in general; we don't worry too much about bacon that is crisp-fried and well drained, or about lean baked ham. We do limit ice cream, desserts, cheese, nuts and peanut butter.

As to milk, we usually tell our patients that if they drink one glass of milk with each meal they probably will not have any trouble in this regard. If they drink larger quantities of milk, which of course many teen-agers do, we suggest that in amounts over three glasses they drink skim milk, and eliminate as much of the butterfat content as possible.

It is not necessary to be too rigid with dietary factors, because they vary greatly from one person to the next. Some persons can eat certain foods, particularly chocolate, and have an accentuation of their acne within 12 to 24 hours.

Local or topical therapy—In addition to the dietary restrictions, we prescribe some local or topical therapy. The most satisfactory agents are various types of sulfur derivatives or sulfides. Common N. F. lotio alba is probably the most widely used local medication and is generally quite satisfactory. In many instances, N. F. lotio alba has to be strengthened and made more astringent, depending on the amount of seborrhea. There are several modifications of lotio alba which provide effective astringent keratolytic lotions.

The object of most local therapy for acne is to produce a desquamating or peeling effect. This is done to reduce the degree of hyperkeratotic plugging of the follicular orifices in order to allow proper drainage of the sebaceous glands to the surface of the skin.

Another effective lotion utilizes alcohol as a menstruum for salicylic acid and resorcinol. Such lotions are very satisfactory for use during the day because they do not leave a film on the skin. Several types of cosmetic bases are also available. These are not completely adequate for a single local therapeutic regimen, but they are valuable adjuncts, especially for women.

In cases involving a lot of cystic reaction and pustulation in which one desires to produce a greater degree of keratolysis and drainage as quickly as possible, hot applications of Vleminckx's solution are quite satisfactory. This is a solution of calcium sulfuret, a preparation which when diluted with water and applied to the skin has a marked keratolytic and astringent effect. Although its odor is rather offensive, it does have a very beneficial effect when used for a week or 10 days. It is particularly helpful for people who have done nothing about their acne and have a great deal of cystic reaction, pustulation and draining subcutaneous sinuses.

Vitamins—In certain types of acne, particularly those in which the papular elements seem to predominate, with a lot of comedones, large doses of vitamin A are beneficial. We now utilize the water-soluble type of vitamin A and usually prescribe from 75,000 to 100,000 units a day. To be effective, vitamin A therapy must be given for a month to six weeks before one can fairly evaluate any results. If a patient is to be maintained on vitamin A, it is better to have him take it for two or three months, then stop it for a month before resuming treatment with it. I have not had any difficulties with vitamin A therapy, although certain manifestations have been reported from excessive vitamin A.

Vitamin B complex is particularly helpful to those patients whose acne has a marked seborrheic complex. Crude liver extract administered orally is a satisfactory source of vitamin B, as is brewer's yeast; the latter is a handy and relatively inexpensive way of taking vitamin B complex. The riboflavin fraction of B complex may be a more specific remedy for seborrheic dermatitis and seborrhea than

any of the other components, but usually supplemental riboflavin is unnecessary.

Hormonal therapy—Hormone treatment of acne has come into vogue in the last 10 years, and for some patients estrogenic supplemental treatment is most beneficial. Estrogenic therapy is particularly advisable for girls in their late teens, twenties and thirties who still have acne. I do not think one is justified in giving estrogenic therapy to anyone under 19 or 20 years of age and certainly not if there are any aberrations in their menstrual cycles. A great many girls and women have marked aggravation of acne three or four days before and during their menstrual periods. As soon as they have finished menstruation, during the first half of their cycle, their acne is apt to improve. To help in this direction we give them supplemental estrogenic substance during the intermenstrual period. We usually start with one of the estrogenic substances such as PREMARIN®, stilbestrol or sulestrex, and continue this treatment for about 21 days. Then we discontinue the estrogens and start them again following the cessation of the patient's next menstrual period. Large doses of estrogen are usually not required; for example, 0.25 mg. to 0.50 mg. of stilbestrol, 0.625 mg. of Premarin or 1.25 mg. of sulestrex is an adequate daily amount.

Occasionally, estrogenic treatment causes a delay in the next menstrual period. Cessation of estrogenic therapy usually brings the periods back to normal in one or two cycles. As far as I know, there is no harm in giving small amounts of estrogenic substances in this manner. Very often it is not necessary to prolong estrogenic therapy more than three or four months. The dosage is gradually reduced to the point where the patients discontinue estrogens entirely and manage satisfactorily.

In some males, particularly those with marked cystic acne, estrogenic supplemental treatment is also beneficial. The dose is about the same as for females, namely, 0.5 mg. of stilbestrol, or 0.625 mg. of Premarin every day for 30 to 60 days. I have not seen any undesirable side reactions when that amount of estrogenic substance is given for two or three months. Occasionally a boy will have a little enlargement of the breast tissue, but nothing more than that, and again, cessation of the estrogenic substances produces a reversal.

In conjunction with hormonal therapy one should mention thyroid extract as a supplemental type of therapy.

Antibiotics and toxoids—Antibiotics are beneficial in certain instances, especially when there are large pustular elements. In deep cystic acne, with multiple areas of dissecting subcutaneous abscesses that drain, antibiotic therapy for a month to six weeks is helpful. I have also been administering some of the longer-acting penicillin derivatives such as BICILLIN® by injection once every five to seven days. In other instances, TERRAMYCIN® or AUREOMYCIN® seems more helpful, but the cost goes up considerably when one tries to maintain that kind of therapy. In some instances sulfonamide combinations seem beneficial, but I think antibiotic therapy is important in treating certain cases of severe acne.

Vaccine therapy of resistant pustular or cystic acnes should be mentioned. One can utilize a stock vaccine which contains *Staphylococcus* and *Streptococcus* or just *Staphylococcus*. There are mixed types available, so-called acne vaccines, but I am not entirely convinced that they have any advantage over a straight *Staphylococcus* vaccine. In some instances an autogenous vaccine may be more effective, but here again vaccine therapy alone is not sufficient. It must be used as a supplement to the other agents mentioned.

Physical therapy—Irradiation therapy properly given in weekly fractional amounts, within certain known set limits, is a very satisfactory and safe procedure. Irradiation can be given to the face, forehead, shoulders and anterior chest. It is only fair to say that irradiation therapy may not be as widely used in the treatment of acne today as it was 10 or 15 years ago. This may be due to a belief that irradiation is rather ineffective. But perhaps we are treating acne a bit differently now and need not rely on irradiation as much as we did formerly.

Another physical adjunct to therapy is cryotherapy, a method of producing desquamation of the face or the back. Dry ice in the form of

a slush with acetone is used weekly, biweekly, every second or third week or once a month, as an adjunct to topical therapy to produce desquamation and peeling. Cryotherapy also helps to control some of the deep inflammatory reactions, but the exact mechanism is not known. It is especially useful when one handles a large number of acne patients—it is convenient, relatively quick and effective.

Ultraviolet light also produces desquamation and peeling. Many patients note that their acne is much better when they get out into the sun, get sunburned and desquamate themselves. Controlled ultraviolet therapy may be used as an office procedure for this same purpose.

We have at times also caused peeling with certain caustics, such as trichloroacetic acid, and also with phenol. Properly controlled, correct percentages of trichloroacetic acid cause localized peeling in areas which involve old scars.

Surgical measures—Scarring is not an inevitable sequel to acne. Deep cystic lesions almost always result in scarring, but superficial, papular, inflammatory and pustular lesions, if left alone, will not in general produce scarring. It is necessary to emphasize this, especially to the parents of the patient or to the child himself. Much of the damage and scarring from acne is mechanical—it results from the trauma that the person inflicts on his or her skin by trying to squeeze out the pimples and get rid of the blackheads. To do this, patients use bobby pins, hairpins, fingernails—anything to get rid of these pustules. Some women, and men, too, spend a good deal of their time in front of the mirror every day squeezing out as many pustules and blackheads as they can. This is one reason why certain minor surgical procedures are also of value in the proper handling of acne.

By making a proper small incision in the dome of a deep cyst, little or no scarring is produced and drainage is adequate. With deep cystic lesions, cauterization of the wall of the cyst helps to contract these spaces much more rapidly and produces less scarring. To cauterize these, one can use liquefied phenol, followed by alcohol neutralization or silver nitrate. This is a minor but important surgical procedure. For patients having a lot of comedones on their faces it is preferable for the doctor to open many of these by making a small puncture in the orifice and then to use a comedo extractor. With this procedure there is much less likelihood of mechanical trauma to the skin.

BOOKS RECEIVED

New books received are acknowledged each month. As space permits, books of principal interest to our readers will be reviewed more extensively. Reviews and additional listings will be found in this issue starting on page A-116.

Hernia; The Pathologic Anatomy and Their Anatomic Repair of the More Common Hernias. By Chester B. McVay, M.D., Clinical Professor of Surgery and Associate Professor of Anatomy, The University of South Dakota School of Medical Sciences, Vermillion. Edited by Alton Ochsner, M.D., The William Henderson Professor and Chairman of the Department of Surgery, The Tulane University of Louisiana School of Medicine, New Orleans. 40 pages, illustrated. 1954, Charles C Thomas, Springfield, Illinois. $4.75.

The 1954-1955 Year Book of Drug Therapy. Edited by Harry Beckman, M.D., Director, Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee, Wisconsin. 592 pages, illustrated. 1954, The Year Book Publishers, Inc., Chicago. $6.00.

Lobotomy—A Clinical Study. Reported by A. Miller, M.D., Clinical Teacher, University of Toronto Department of Psychiatry, Toronto, Ontario. 107 pages, illustrated. 1954, Ontario Department of Health, Toronto.

Transactions of the American College of Cardiology. Edited by Bruno Kisch, M.D., Robert P. Glover, M.D. and Ashton Graybiel, M.D. Vol. 3, 1953. 256 pages, illustrated. 1954, American College of Cardiology, New York.

Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract

JOHN RUSSELL TWISS[1] AND ELLIOT OPPENHEIM[2]

New York University Post-Graduate Medical School, New York

HISTORY AND PHYSICAL EXAMINATION

The History

SINCE a well-taken history is an essential part of the diagnostic investigation, a review of procedures seems merited.

The Chief Complaints

Pain is the chief complaint of most patients with gallbladder disorders; pain may also be a prominent feature of those with liver disease. An intolerance to roughage and foods high in fat is frequent. Occasionally there is an apparent allergic reaction to certain foods. Other symptoms are listed in table 1.

The usual symptomatology of chronic liver disease, not associated with pain or with gallbladder disease, is deserving of a brief review. Generally speaking, the symptoms which may be found with chronic liver disorders are headache, anorexia, nausea, discomfort after meals, bad breath, coated tongue, constipation or diarrhea, epigastric or right upper quadrant pain or tenderness, and mental depression. With more advanced disease there may be epistaxis, hematemesis, melena, emaciation, cachexia, enlargement of the abdomen, ankle edema, cerebral symptoms, coma, or death. Any of the above symptoms indicates the need of a detailed history, especially in regard to the use of alcohol, starvation, cardiac disease, or exposure to hepatotoxic materials. Occupational hazards or dietary factors which might have contributed to the involvement of the liver should also be kept in mind. Details can be found in the chapters on these subjects.

Discussed in later chapters are: the *early diagnosis of acute liver disease; acute yellow atrophy* or acute necrosis of the liver (is deserving of mention because of its abrupt onset and frequently rapidly lethal clinical course); *chronic pancreatitis* (may give intermittent attacks of abdominal pain, epigastric or left upper quadrant in location); *chronic liver disease;* hemorrhage, which is one of the more serious and frequently terminal events in *cirrhosis of the liver* (the hemorrhage may be evidenced by nosebleed, vomited blood or tarry stools).

Pain

Character—Pain may be dull, colicky, aching, constant, or intermittent. Colicky pains are most apt to occur as the result of the sudden overdistention of the biliary tract caused, for example, by an impacted stone or by a spastic common duct sphincter. A dull, constant, prolonged type of pain may be produced by a gradual distention of the biliary tract, such as that resulting from a fibrotic or neoplastic common duct stricture. A constant

[1]Assistant Professor of Clinical Medicine; [2]Assistant Professor of Medicine, both of New York University Post-Graduate Medical School, New York.

Chapter 1 of the book, "Practical Management of Disorders of the Liver, Pancreas, and Biliary Tract," published January 1955 by Lea & Febiger, Philadelphia.

type of pain may also occur as the result of neoplastic or inflammatory conditions of the gallbladder, liver, or pancreas.

Intrahepatic pain is usually referred to the epigastrium or right upper quadrant, with radiation to the back. The character is usually aching; however, it may become severe with overdistention of Glisson's capsule. The enlarged liver of extrahepatic biliary tract obstruction is seldom very painful, unless it is associated with active infection.

Onset—The onset of biliary tract pain commonly occurs several hours after a heavy meal, particularly one rich in fats. Pancreatic or liver pain may occur after alcoholic excesses. The ingestion of roughage may precipitate attacks, especially in those having gastric hyperacidity or duodenitis. Colic, on the other hand, may occur for no particular reason. It can and frequently does waken the patient out of a sound sleep.

Frequency—Frequently recurring attacks of pain, particularly if severe, suggest the need of surgical intervention. The intervals between attacks of pain should be noted.

Location—Pain occurs with equal frequency in the epigastrium and in the right upper quadrant in proved gallbladder disease. The pain of liver disease is more commonly in the right upper quadrant; it may, however, occur in the epigastrium.

Radiation—The pain of gallbladder disorders often radiates to the back, especially to the region of the right scapula. With diaphragmatic irritation there may be pain in the shoulder or difficulty in breathing. Radiation to the precordial region may occur with overdistention of the common or cystic ducts. Generalized pain of the upper abdomen may occur. The pain of pancreatic disease may be boring in type and localized in the epigastrium or the left upper quadrant. The pain may radiate directly to the left lumbar region, the precordium, or the left lower quadrant.

Duration—Pains of short duration may be functional in origin, particularly if relieved by nitroglycerin, amyl nitrite, or intravenous aminophylline. Attacks severe enough to require opiates for relief may be assumed to be organic in origin.

Aggravating factors—Pains originating in the biliary tract may be aggravated by food high in fat, as well as by irritating types of foods such as sauces, condiments or roughage. Similar effects may result from nervous tension, worry, excitement, or undue fatigue.

Means of relief—The means of relieving biliary tract pain consists of antispasmodics, narcotics and heat. The persistent pain of an overdistended biliary tract owing to a hypertonic dyskinesia may be relieved by a bland diet. Pain associated with gastric hyperacidity or duodenitis responds well to antacids. The interval between the onset of acute pain and jaundice is of interest. With lower common duct obstruction, associated with the absence of the gallbladder or cystic duct obstruction, jaundice follows pain within 12 hours. With a functioning gallbladder, however, the onset of jaundice may be delayed three or four days.

Associated Symptoms

Loss of weight may occur with advanced organic disease of the pancreas, liver or extrahepatic biliary tract. Loss of strength, anorexia, cachexia and anemia may also occur, especially with malignancy or cirrhosis of the liver. A preceding alcoholic history with concomitant abdominal enlargement, ascites, edema or hemorrhage suggests cirrhosis. In this clinic, however, the most common cause of loss of weight is chronic cholecystitis. With this condition the patient usually volunteers the information that she is "afraid to eat." Other associated symptoms are listed in table 1.

Constipation is one of the most frequent symptoms associated with chronic disease of the biliary tract. Its presence in the aged and in those with a spastic irritable colon has been mentioned.

The *past history* should especially note recurrent digestive attacks, which indicate chronic disease of long standing. Furthermore, the presence of other foci of infection may be of significance, especially those in the sinuses, tonsils, teeth, appendix and urinary tract.

A review of *past illnesses* and *operations* may give information having a direct bearing on the presenting symptoms. An arthritis of

the spine, for example, may be responsible for recurrent attacks of pain in the right or left upper quadrants. Chronic heart or renal diseases may also give pain or other digestive symptoms simulating biliary tract disease. The frequent association of organic disease of the gallbladder, liver and heart should always be kept in mind.

A *systemic review* of the usual type, concerning the gastrointestinal, cardiovascular, respiratory and genitourinary systems, may also give information having a bearing on the digestive symptoms. The well-known relationship of symptoms suggesting biliary tract disease to other systems is discussed in the appropriate sections.

The *family history* may be of interest in relation to longevity and diseases of parents and siblings. The possible relationships of jaundice, arthritis, hypertension or neoplastic disease afford, at times, leads of value.

The immediate family of the patient is of even greater importance, especially in regard to the health and compatibility of the marital partner. Lack of proper sexual or social adjustment frequently leads to digestive disorders, as do a multitude of other situations relative to the family. Financial worries and responsibilities which either partner is unwilling or unable to meet form common sources of difficulty. Physically or mentally inadequate children may also cause digestive symptoms in the parents.

The *personal history* should include a review of the patient's occupation, his attitude and adjustment to his work, his financial compensation and possible incompatibility with his associates or superiors. Problems here may be responsible for digestive symptoms.

Dietary and hygienic habits should be reviewed, as excessive smoking and alcoholic intake may play an important part in producing digestive symptoms. Furthermore, the same result may be obtained from the excessive use of irritating types of foods, such as condiments, sauces, spices or salted foods. Digestive disorders may also result from irregular eating habits, such as "skipped" or delayed meals, eating when nervous or unduly fatigued, "bolting" of food, or the resumption of mental or physical labor immediately after a meal.

A common-sense correction of any detrimental habits or situations having an apparent adverse effect may be far more efficacious than drugs in the relief of symptoms.

The summary chart of the diagnostic investigation used by us is shown in table 1.

The Physical Examination

The primary consideration in the physical examination of the patient having symptoms of biliary tract disease should be a detailed investigation to determine the presence of any systemic disease which might be responsible for the presenting symptoms.

The initial recorded findings should include the patient's age, height, weight, temperature and blood pressure. Under the age of 40, there is a different group of diseases from that in patients over 40. Younger patients are more susceptible to the functional disorders and the acute inflammatory diseases of the liver, whereas the older group show more frequent cholelithiasis, cirrhosis, and malignancy. The weight of the patient should be compared with normal standards. A recent change in weight is usually significant. The recorded temperature may reveal the presence of inflammatory conditions which otherwise might not have been suspected. The blood pressure likewise may vary considerably, from hypotension (which may be associated with asthenia or adrenal disease) to hypertension commonly found in elderly patients.

The general appearance should be noted. Common findings of internal tension are dilated pupils, excessive postcervical tenderness, a spastic tender colon, cold clammy hands, and overactive reflexes. Nutritional disturbances may show as weight loss, anemia or cachexia. Jaundice is sometimes overlooked in artificial light. Abdominal examination may reveal enlargement, vascular disturbances as collateral circulatory changes, or edema. Abnormalities in posture may indicate arthritis. The older cachecic patient with a drawn "hepatic facies" and a protuberant abdomen full of fluid is significant of cirrhosis.

A history of recurrent colds, sinusitis or

TABLE 1

BILIARY TRACT CLINIC

Date .....
Name .....
Address .....
Occupation .....

Age ..... Sex .....
S. M. W. D. .....
Referred by .....

Chart No. .....
Nationality .....
W. B. .....

C. C. ..... *Dur.* .....
Pain .....
Char. .....

1st Attack .....
Last Attack .....
Freq. .....
Duration .....
Hypo. Req. .....
Onset .....
Location .....
Radiation .....
Aggrav. by .....
Relieved by .....

Associated Symptoms:
Jaundice .....
Nausea ..... Headache .....
Vomiting ..... Fever .....
Belching ..... Chills .....
Distention ..... Tender R.U.Q. .....
Fat. Intol. ..... Clay Col. Stools .....
Loss of Wt. .....
Symptoms between Attacks:

P. I. (To be recorded reverse side)
A. Details not covered above
B. Previous treatment
C. Results of treatment
D. Transfusions
Blood or Plasma

F. H.:
Children—No. .....
Ages .....
Misc. .....
Fam. Hist. .....
.....

P. H.:
Illnesses .....
Operations .....

Resp. .....
C. V. .....
G. I. .....
Const. .....
Mucus ..... Blood .....
G. U.:
Menst. X X

Previous Examinations:
Date
X-ray .....
Blood Chem. .....
G. B. Drg. .....
Other .....
.....

Physical Exam.:
Ht. ..... Wt. .....
B.P. ..... T. ..... P. ..... R. .....

Appear. .....
.....
Norm. ... Sthenic ... Asth. ...
Head
Eyes
N. & T.
Heart
Lungs
Abdomen
Tenderness
Palp. Liver
Palp. Spleen

Extrem.
Reflexes
Tentative Diagnosis:

Assoc. Conditions .....
.....
Final Diagnosis:

Advise: Date:
X-ray
Duod. Drg.
Blood Chem.
Other
Hosp. Adm.
Follow-up

sore throats justifies a detailed nose and throat examination. Dental caries or suspicious teeth justify a similar investigation. A rectal and, if necessary, a proctosigmoidoscopic examination may reveal evidence of rectal, prostatic, or colonic pathology.

A careful examination of the skin may reveal evidence of biliary tract disease. The facies may show multiple dilated venules or spider angiomas (figure 1). The upper lids may show the yellowish plaques of cholesterol known as xanthelasma palpebrarum. Similar masses are sometimes found in the creases of the palms of the hands (xanthoma planum) or as nodular lesions of the elbows (xanthoma tuberosum). These lesions may occur with hypercholesterolemia, xanthomatous biliary cirrhosis or diabetes mellitus. The slate-colored jaundiced appearance of hemochromatosis should also be mentioned. Evidence of collateral circulation may be found in the dilated veins of the thorax or abdomen (figure 2). Hemorrhages occur at times, subcutaneously or from the mucous membranes, in patients deficient in prothrombin. On the legs there may be purpuric rashes, varicose veins or varicose dermatitis.

Examination of the neck may reveal enlarged nodes, which are sometimes of metastatic origin. Biopsy of such a gland may yield valuable information.

The chest should be examined for evidence of any pathologic condition of the heart and lungs. Careful inspection and palpation of the breasts is essential. The absence of chest hair and presence of gynecomastia is sometimes found in males with cirrhosis of the liver. The axillae should be palpated. Roentgen ray study

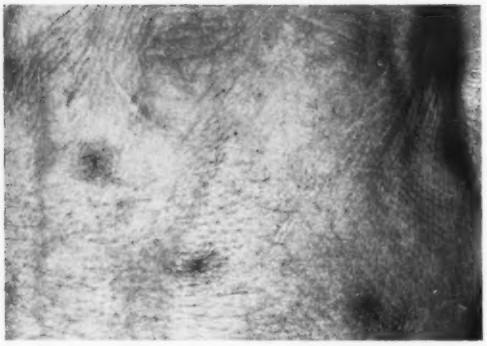


FIGURE 1. Spider angioma.

is indicated in all questionable cases, especially where pulmonary tuberculosis, metastases, fluid effusion or organic disease of the heart is suspected.

Abdominal examination may reveal ascites, hepatomegaly, splenomegaly or pancreatic cysts. Abdominal masses should be differentiated from the diffuse enlargement due to ascitic fluid.

Among the causes for an enlarged liver, French* has listed the following:

Venous congestion—cardiac cirrhosis
Obstruction of common bile duct
Suppuration of liver—multiple abscesses
Cirrhosis of the liver
Splenic anemia (Banti's syndrome)
Hemochromatosis (bronzed diabetes)
Syphilis of the liver
Chronic perihepatitis
Carcinoma of the liver—primary or secondary
Sarcoma of the liver
Fatty liver
Lardaceous liver
Polycystic liver

Fluid, if present in large amounts, usually gives a generalized abdominal enlargement with bulging of the dependent parts in the prone or upright positions. With an appreciable amount of abdominal fluid, there are usually a fluid wave, flatness in the flanks on lying down, and shifting dullness on change of position. The liver may be ballotable, giving a "bouncing" sensation on deep pressure. There may be edema of the legs or scrotum, with or without ascites. French has summarized the various causes of ascites and enlargement of the spleen.

With an apparent splenomegaly, French* states that the following possibilities should be considered in differential diagnosis:

Kidney tumors:
Perinephritic inflammation or abscess
Suprarenal tumors
Carcinoma, splenic flexure of colon
Pancreatic tumors: Cysts, carcinoma
Gastric neoplasms
Ovarian tumor
Tuberculous peritonitis
Fecal masses of colon

French* lists the following possibilities as etiologic factors in splenomegaly:

A. Spleen greatly enlarged:

Leukemia
Malaria
Polycythemia
Splenic anemia
Gaucher's disease
Still's disease
Familial acholuric jaundice
Schistosomiasis

B. Spleen moderately enlarged:

Pernicious anemia
Rickets
Congenital syphilis
Cirrhosis of the liver
Portal hypertension
Typhoid fever
Relapsing fever
Typhus
Septicemia
Embolism

Frequently a satisfactory abdominal examination is impossible without a paracentesis. The fluid removed is of great value in differential diagnosis and should have a detailed laboratory investigation. Exudate fluid, hemorrhagic or otherwise abnormal in appearance, may be obtained in malignancies and in other pathologic conditions.

A detailed study of the liver should be recorded at the time of the initial examination. A palpable liver is not necessarily enlarged; a ptosis may be present. Enlargement is noted as being localized or diffuse. The consistency of the liver is described. The smooth enlargement of the liver adjacent to the gallbladder found with Riedel's lobe should not be considered a pathologic finding.

In early stages of liver disease there may be found a diffusely enlarged fatty liver. The enlarged, soft and frequently tender liver may be found in acute or chronic parenchymal disease of this organ or in cases of extrahepatic biliary obstruction. The hard nodular liver suggests cirrhosis or malignancy.

Tenderness of the liver associated with chills and fever indicates active inflammation. Localized masses may be found with malignancies, abscesses, or cysts. Malignancies are

*FRENCH, H.: Differential Diagnosis, 6th ed. Baltimore, Wood, p. 471, 1945.

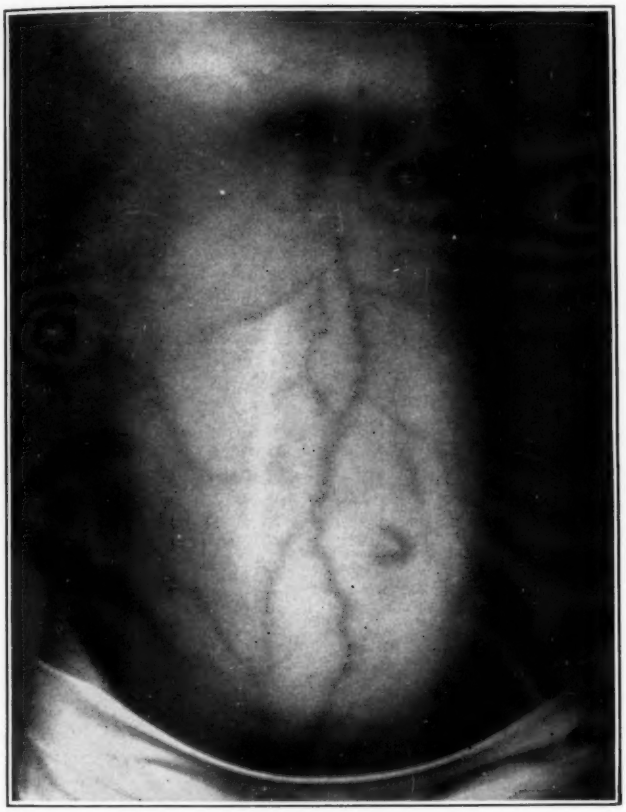


FIGURE 2. Collateral circulation of distended abdominal wall, showing the dilated veins by infrared photography.

usually secondary to a primary lesion elsewhere in the gastrointestinal or biliary tract.

Among the less common causes of liver disease are parasitic infections. Cirrhosis may be due to schistosomiasis in countries where this disease is prevalent. Biliary tract obstruction may occur with this condition or with worms from the gastrointestinal tract, such as *Ascaris lumbricoides*. Hydatid cysts or amebic abscess may occur in the liver.

The size of the liver should be carefully noted daily in the acutely ill patient, since acute necrosis may supervene in almost any type of liver disease. An actual diminution in size within a few days may be demonstrated by palpation and percussion in these patients.

In the chronically ill patient the enlarged gallbladder is seldom enlarged or palpable preoperatively. Among the causes of an enlarged palpable gallbladder should be mentioned hydrops and empyema of the gallbladder. Malignancy of the gallbladder may give a palpable mass in the right upper quadrant. The palpable Courvoisier gallbladder is usually due to stricture, inflammation or malignancy involving the head of the pancreas or the common bile duct.

A tender mass in the region of the gallbladder may be due to an acute cholecystitis. In these patients there is commonly a prolonged history of recurrent indigestion, because of the presence of a chronic cholecystitis and cholelithiasis. The elderly patient with a gangrenous gallbladder may have acute tenderness without fever or leukocytosis.

Splenomegaly may occur with cirrhosis of the liver as the result of portal hypertension. Other causes of splenomegaly should be ruled out. There may be associated hepatomegaly, ascites and varicosities of the esophagus or other parts of the gastrointestinal tract.

The physical findings in the patient with jaundice may be of assistance in differential diagnosis. In hemolytic prehepatic jaundice the icterus is not pronounced, and there may be splenomegaly.

With acute hepatic types of jaundice, enlargement and tenderness of the liver are common. In chronic types of hepatic jaundice there may be both hepatomegaly and splenomegaly, *i.e.*, cirrhosis. With acute hemorrhagic pancreatic necrosis, shock, cyanosis and tenderness over the gallbladder and pancreas are prominent features.

Occasionally children are seen with jaun-

PLATE II. Xanthomatous infiltrations.

A. Yellowish-red lesions on the extensor surface of the forearms.

B. Localization in the creases of the fingers.

C. Xanthelasma.

D. Xanthoma diabeticorum.

E. Xanthoma tuberosum lesions are common on joints and in the tendon sheaths.

(LEWIS, G. M.: Practical Dermatology, p. 238, plate 87, W. B. Saunders, 1952.)

dice or hepatic enlargement. Excluding the transient icterus neonatorum, jaundice in the newborn is usually caused by some obstruction of the biliary tract, such as congenital absence of the biliary ducts, intra- or extrahepatic stricture, cystic disease of the common duct, or, rarely, by the presence of inspissated mucus. Cirrhosis may also occur in children.

With the jaundice due to congenital syphilis, there may be a hepatomegaly, "snuffles," and later Hutchinson's teeth and interstitial keratitis. Jaundice may also be associated with enlargement of the liver, secondary to malignancies which are sometimes retroperitoneal in origin. Among other causes of jaundice to be considered are blood dyscrasias. Pick's disease or adhesive pericarditis may be associated with generalized edema.

An excellent review of physical findings in diseases of the liver, gallbladder and pancreas has been published recently by Butler and Bargen.*

In summary, the carefully taken history and a complete physical examination should serve as the basis for a tentative diagnosis. This diagnostic impression, in turn, indicates the type of laboratory and roentgen ray studies which are necessary to confirm the diagnosis.

*BUTLER, D. B. and BARGEN, J. A.: Abdominal masses. III. Diseases of the liver, pancreas and spleen. Gastroenterology 19:32, 1951.

Editorials

Postgraduate Medicine

Editor-in-Chief:
CHARLES W. MAYO, M.D.

Contributing Editor:
MORRIS FISHBEIN, M.D.

Assistant Editor:
SYLVIA COVET

MEDICAL LIBRARY AID

READING a recent article by Dr. Edwin Pulaski[1] has set us to brooding over medical libraries and the state of medical literature generally. Dr. Pulaski says that "the medical library should be in the central necessity core of medicine" and by so saying he implies that the library has not yet reached that hoped-for estate.

It seems to us that many physicians do not make as much use of medical libraries as they would like because they feel they do not have sufficient time to give to it. This may worry their consciences somewhat at times, for they remember the admonition of their medical school professors on the value of the literature in keeping a physician up-to-date. They may also be aware of Osler's remark that "to study the phenomenon of disease without books is to sail an uncharted sea," and wonder how Osler could possibly keep up with all his patients and still have time for reading.

The number of medical libraries, both large and small, in operation in the United States seems to be prima-facie evidence that at least some people use medical libraries and find them valuable enough to support. In addition, the "Package Library" services of the American Medical Association and the American College of Surgeons and the extension work of state and medical school libraries, intended for physicians remote from medical collections, are well patronized by physicians throughout the country. It would appear that medical libraries *do* furnish some doctors with the help they need, and the regret is that a misconception of the difficulty of using a library prevents some others from taking advantage of the available services.

We believe library aid is most useful when it takes the form of (1) keeping the practitioner informed of what is being published, through published catalogs, indexes and bibliographies; (2) making the literature available to him by loaning him copies of it, borrowing it for him from another library, if necessary, or getting microfilms or photostats for him to read; and (3) making preliminary investigations into the published works for specific subjects needed by the individual physician.

But the help which a physician gets from a medical library is proportional to his knowledge of how to use it, and unfortunately many doctors, because of their lack of experience, are fumbling and inept in their attempts to obtain what they need from medical literature. Although much of this ignorance of the basic principles of using medical libraries can be blamed on the medical schools which have not taught this art adequately to the student,

it is nevertheless true that a practitioner who wishes to do so can rectify the situation in a few hours of concentrated study. No surgeon would attempt an operation without previous experience on the cadaver; yet he may try to use a library without studying the literature tools. What he needs to do is to sit down with copies of the *Current List of Medical Literature*, the *Quarterly Cumulative Index Medicus*, *Excerpta Medica*, and a few good review journals, and examine each one carefully. Which list journal articles only? Which just list the literature and which give summaries of it? Which refer only to individual pieces, and which survey whole chunks of the field? Which are the most up-to-date; which come out most frequently? A knowledge of the answers to these questions will save the inquirer much frustrating, hit-or-miss searching.

Medical libraries cannot be of the greatest help to the physician unless he is willing to help both himself and them. If the doctor gives time and thought to mastering the guides to medical literature, and if he expects occasional help from the library staff, he should also remember that this matter of aid is a two way street. He can help the library by advice on book selection, by seeing to it that the library has adequate financial support and, for the long run, by steering promising students into medical librarianship. We in this country may well be grateful for our good fortune in having a strong national library of the medical sciences, the Armed Forces Medical Library in Washington; in having a vigorous professional group, well represented by the Medical Library Association; and in having, on the whole, the kind of librarians who adhere to what John Shaw Billings used to call the "hodcarrier" theory of librarianship, wherein the good librarian is one "who brings together the bricks made by one set of men in order that another set of men may build therewith . . . (and) he is apt to take quite as much pride and satisfaction in the resulting structure, provided it be a good one, as if he built it himself."

REFERENCE

1. Pulaski, E. J.: The user looks at the library. Bull. M. Library A. 42:421-425 (October) 1954.

THE COSTS OF MEDICATION

The pharmaceutical industry, and particularly the pharmacist who conducts his efforts through the drugstore, are concerned with the high cost of much modern medication. These costs reflect factors which are not clear to the majority of persons who purchase remedies over the counter or receive them through physicians' prescriptions. Among other factors, the increased costs represent the cost of research and the increasing costs of labor and taxes. As examples, one manufacturer put $30,000,000 into the first production of cortisone; another manufacturer invested $20,000,000 in research leading to the mass production of penicillin. The records of the pharmaceutical manufacturers note many millions of dollars spent in research which did not ultimately yield a marketable product.

In Great Britain discussions have been going on for some months between the Ministry of Health and the pharmaceutical industry about the prices which the government should pay for drugs bought under the National Health program. The cost of drugs represents one of the most important items in the administration of the National Health program. Attempts have been made to have physicians prescribe pharmacopoeial rather than proprietary preparations, and the Ministry has issued a regulation to the effect that doctors should not be free to prescribe proprietaries unless the prices charged for them have been approved by the Ministry in negotiation with the manufacturers. In its attempt to carry out this ukase, the Ministry of Health had great difficulty in determining what were suitable prices for proprietary preparations.

The London *Times* took note of the fact that the bread-and-butter business of pharmaceutical firms must help to support their work in developing new drugs. Not all British pharmaceutical firms participate in research and development. The London *Times* says, "The most rapid advances in pharmaceutical research have been made in countries such as the United States and Switzerland, where profit rates have been higher than in Britain."

Yet it notes also that there is a danger that pharmaceutical research may be rendered so unattractive in Great Britain and so unprofitable that this important field of research may be abandoned by one company after another. "It would be ironical if the introduction of the National Health Service was allowed to have this effect."

In July 1954 the *American Pharmacist* published as a complete issue a symposium on the high cost of medication. All of the usual arguments were advanced to the effect that the duration of illness has been greatly shortened by the use of modern medicaments, that the costs of research enter into the question, that one uses the medicaments in small amounts and for a shorter time and that they have saved lives in untold numbers. Actually the costs of medication are far less than the costs of burial, and the results are more significant in yielding happiness. However, none of these arguments and even the argument that luxuries cost far more than lifesaving and disease-preventing medications is likely to influence the purchaser.

Technics eventually may be developed in which significant contributions by insurance agencies will help to bear a portion of the cost of drugs for the poor. Some have sought a remedy in amelioration of taxation for the sick, yet a formula whereby such taxation could be applied has not yet been forthcoming. Labor costs are not likely to be less and the work of the employed person in the pharmaceutical industry is not likely to be considered too much different from that of workers in other industries or even of workers in hospitals to permit special relationships. The increased labor, shortening of hours and specialization of services that have gone on in the hospitals have contributed tremendously to the costs of hospital care.

One can only join with the London *Times* in its belief that discontinuation or substantial diminution of research in the pharmaceutical industry would be the most regretted of any of the results which might accrue from public resentment against current costs of modern pharmaceuticals.

MORRIS FISHBEIN

SNUFFLES

THE word "snuffle" is an old English term meaning mucus. From this word came sniff, snivel, sniffle or snuffle. When I was a medical student, the word "snuffle" referring to the habits of an infant meant that a special search should be made for the presence of syphilis, and most books which mention the subject even today indicate that snuffles is usually related to that venereal infection.

Now an eminent British physician[1] and his associates have made a special study of 99 infants with snuffles in Bristol, England, and have concluded that there is a regular occurrence of snuffles in about 2.6 per cent of all infants, that snuffles occur slightly more frequently among girls than among boys, and that there is no reason to believe that the symptom is in any way related to syphilis in the vast majority of cases. In most cases snuffles began between the second and twelfth days of life, lasted up to a week; usually the discharge was serous but in some babies it was purulent from the onset. Most frequent complications were breathing difficulties and upper respiratory infections. The vast majority of cases seemed to represent simply an early inflammation or infection of the upper respiratory tract.

Thus do the old impressions of a previous generation disappear with modern scientific study and investigation.

MORRIS FISHBEIN

REFERENCE

1. APLEY, JOHN, LAURANCE, B. and MACMATH, I. F.: Snuffles in the newborn: Frequency, actiology and natural history. Lancet, November 20, 1954, p. 1048-51.

THE HISTORY OF APPENDICITIS

CAREFUL analysis of the history of any disease or procedure in medical science casts light on trends of medical thought. In a recent issue of *Lancet*, Dr. John A. Shepherd[1] contrasts the British and American influences of the last century on procedures in acute appendicitis.

The appendix was recognized as an ana-

tomic structure by the early Egyptians, yet the pathologic changes that may occur in the organ were hardly recognized before the eighteenth century. Apparently in 1736 a surgeon to George II successfully removed the appendix of an 11 year old boy in the course of an operation for a scrotal hernia complicated by a fecal fistula. A French physician, Mestivier, gave the first account of an operation for appendicitis with subsequent necropsy in 1759. Other cases were described in 1812 and in 1824, both in England and in France, but during this period the French surgeon Dupuytren insisted that these infections were diseases of the cecum and not of the appendix. He was supported in his view by German surgeons. In 1827 a French surgeon, Melier, reported six cases; this is believed to be the first paper in which a detailed discussion of appendicitis appears. From this time on various case reports were published, without, however, any really accurate analysis of the condition. Bright and Addison of Guy's Hospital, London, accurately described in 1839 the usual course of appendicitis, but their statements received little attention.

After 1850 the myths of a general infection of the abdomen and a specific disease of the cecum began to disappear. Willis Parker, in 1867, recognized three important stages of acute appendicitis. Disturbed by the difficulty of differentiating between acute inflammation of the appendix and acute obstruction of the intestines, he advised giving a strong cathartic in the belief that bowel movements would be positive evidence of the absence of obstruction. Today this would be recognized as a most hazardous procedure. As late as 1884, British surgeons, including Sir Frederick Treves, were still insisting on utmost caution, but in 1884 Mikulicz asserted that the acutely inflamed appendix should be removed, and a German surgeon named Krönlein was the first, according to Dr. Shepherd, to carry out the suggestion of Mikulicz with some success.

In the United States Dr. T. G. Morton, in 1887, diagnosed acute appendicitis and removed most of the inflamed appendix. This report received scant attention in Great Britain. Then in 1886 Fitz reviewed the confused opinions of pathology held at that time and showed conclusively that right-sided, circumscribed peritonitis was almost always due to disease of the appendix. He wrote, "It seems preferable to use the term appendicitis to express the primary condition," and this appears to be the first occasion on which the term "appendicitis" was used. Fitz disagreed with the dictum of Willard Parker that the operation should be done between the fifth and twelfth days; he advocated operation by the third day. Operative technic was developed by McBurney in 1889, Fowler in 1894, and Deaver in 1898; these papers were followed by Murphy's more extensive contribution in 1904. Dr. Shepherd considers these papers to be landmarks in American medical writings on the appendix, and these definitive discussions became the basis for the principles now followed in this country.

In Great Britain progress in treating appendicitis was hindered by various prejudices much as it was in the United States. Treves, the great British leader, urged the "interval" operation and his views persisted until well into 1900. In 1902 Treves operated on Edward VII but did not remove the appendix, simply draining the abscess. Recently Bett called attention to the fact that Treves lost his own daughter from perforative appendicitis and that operation was not done.

Dr. Shepherd is convinced that British surgeons were overcautious in adopting new ideas and slow to learn the lessons taught by Fitz and others. A similar attitude prevailed in the development of early operative intervention for perforated peptic ulcer. Perhaps the high incidence of fatalities after perforation of the intestine due to typhoid had much to do with the attitude of the British surgeons.

MORRIS FISHBEIN

REFERENCE

1. Shepherd, J. A.: Acute appendicitis: A historical survey. Lancet 2:299 (August 14) 1954.